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# ANNALS OF INTERNAL MEDICINE

VOLUME 11

JANUARY, 1938

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## THE TREATMENT OF RHEUMATOID ARTHRITIS WITH AN INJECTABLE FORM OF BEE VENOM \*

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FOR many generations there has been prevalent among the rural population of European countries and to a lesser extent in America, a belief that the sting of bees is a cure for rheumatism. Beck,<sup>1</sup> in 1935, published a book on this subject and he traced the use of bee sting and bee venom from antiquity up to the present time. Bee-keepers were the first to use bee sting in the treatment of rheumatic conditions and it is only within the past 50 years that physicians have adopted it as a therapeutic measure. The first medical report of its use for rheumatoid arthritis was published in 1859 by Demartis<sup>2</sup> of Bordeaux. Terč,<sup>3</sup> in Austria in 1880, was the first to use bee sting in his practice as a form of therapy for rheumatoid arthritis and neuritis, and he so treated a large number of patients. He published several favorable reports concerning its value but was unable to arouse much enthusiasm among the members of the medical profession. During the past 30 years bee sting therapy has been used in European countries with increasing favor.

In 1928, Pollack,<sup>4</sup> in Munich, and Kretschy<sup>5</sup> in Vienna produced an injectable form of bee venom. This product is now made in the chemical laboratories of Dr. August Wolff in Bielefeld, Germany, under the name of "Apicosan." The composition and method of preparation of "Apicosan" have not as yet been published, but the authors claim that it "contains the natural secretion of the honey bee in physiological saline solution." Favorable reports of its use for the various forms of rheumatism have been published by physicians in Berlin, Vienna and Geneva.

\* Received for publication March 10, 1937.

From the New York Hospital, and the Department of Medicine of Cornell University Medical College, New York City.

The bee venom used in this experiment is a preparation called "Apicosan" manufactured by Dr. August Wolff, Bielefeld, Germany, and dispensed in the United States through A. W. Kretschmar, Inc., New York City.

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M.K.

However, in spite of the many articles that have appeared on the use of bee venom for the treatment of rheumatism there is hardly one that presents evidence of a scientific application of this form of therapy. In most instances, the type of rheumatic disease studied is not clearly defined, the number of patients treated is small, and only generalized statements regarding the results are given.

#### PRESENT STUDY

The present study was undertaken in order to determine the merits of bee venom in an injectable form (*Apicosan*) in the treatment of rheumatoid arthritis. The patients included in this report were all ambulatory and were treated in the Arthritis Clinic of the New York Hospital. The patients were intelligent and coöperative and were permitted to pursue their usual occupations. An attempt was made to select only patients in whom a focus of infection had been removed some time previously, or in whom none had been found. A few patients were included, however, who had diseased tonsils, the removal of which was contra-indicated. Many of the patients had undergone various forms of therapy without relief.

The patients included in the present study were divided into four groups. One group comprises patients with a markedly active and advanced form of arthritis—deformities such as ulnar deviation and partial or complete ankylosis of one or more joints characterize this group. A second group includes patients presenting the typical picture of well developed rheumatoid arthritis with the characteristic periarticular swelling of the joints, usually including fusiform fingers. A third group comprises those who complained of severe pain in the joints but who failed to show any evidence of arthritis at the time of examination, other than tenderness and stiffness of the joints. In the tables these three groups have been represented by the symbols +++, ++, and +, respectively. All of these patients were found to have an elevated corrected sedimentation index on admission. There is a fourth group, similar to group three except for the fact that the patients had a corrected sedimentation index within the normal range.

Forms of treatment supplementary to the bee venom injections were limited to a minimum. An unrestricted diet, high in vitamins, was usually recommended. Acetyl salicylic acid was frequently prescribed for the relief of pain and patients were advised to apply heat to the affected joints. Cod liver oil was given in many cases.

One hundred patients were studied—25 male and 75 female. The youngest patient was 21 years of age and the oldest 74 years. Thirteen patients were under 30 years of age, fifty-seven ranged in age from 30 years to 50 years and thirty were over 50 years of age.

The duration of the arthritic symptoms ranged from three weeks to 60 years. Thirty-six patients had had arthritis for one year or less, 38 patients between two and five years, and 26 patients more than five years.

Because of the tendency of patients with rheumatoid arthritis, who have been relieved of their symptoms, to suffer relapses or to develop transitory pains in the joints, we have not classified any of our cases as *cured*, being content to use the word *improved*. Improvement was judged by a fall in the corrected sedimentation index, if previously elevated, and an alleviation of the clinical symptoms. Care was exercised not to confuse temporary changes due to climatic or other varying conditions with more lasting ones. No patient has been included who has not been under observation for at least two months and many have been followed for a year or more.

#### METHOD

All injections were given intradermally. The site selected depended upon the location of the most painful joints. The skin was cleaned with alcohol and wiped dry with benzene. *Apicosan* comes in four different concentrations: N, I, II and III. Strength N is a 1:10,000 dilution of concentration I. One c.c. of concentration I is said to contain the venom of one bee sting, 1 c.c. of concentration II, of three bee stings, and 1 c.c. of strength III, of nine bee stings.

The initial or test dose was 0.1 c.c. of concentration N, injected slowly intradermally forming a wheal. If no reaction followed this injection then 0.1 c.c. of concentration I was given, at the next visit. The treatments were continued at weekly or biweekly intervals, increasing 0.1 c.c. at each visit. Only 0.1 c.c. was put into a wheal and the wheals were placed about one inch apart. When a patient had received 0.5 c.c. of concentration I, or 5 wheals, he was given 0.1 c.c. of concentration II which was increased to 0.5 c.c. and then concentration III was started. The dose was then increased 0.1 c.c. at each visit until the patient was receiving one ampoule of concentration III. All injections were watched for five minutes. If large pseudopodia developed in the wheals, they denoted sensitivity and the dose was not increased for several visits. With one exception, only those patients were included in the study who had received six or more injections.

The sedimentation test used in this study was that recommended by Rourke and Ernstene,<sup>6</sup> and the figure indicating the sedimentation rate is known as the *corrected sedimentation index*. An index of 0.4 or less was considered normal.

#### RESULTS

One hundred patients with rheumatoid arthritis were treated with intradermal injections of bee venom (*Apicosan*) and 73 showed definite improvement, as judged by a fall in the corrected sedimentation index and an alleviation of the clinical symptoms (table 1). Seventeen of these were found to be entirely free of symptoms six months to a year after the treatments were discontinued, 18 continued to have mild transitory pains only and 38 were moderately improved.

TABLE I

Results of Treatment with Bee Venom (*Apicosan*) of 100 Patients with Rheumatoid Arthritis

Severity of Disease	Number of Patients	Markedly Improved		Moderately Improved		Total Improved		Unimproved	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
+++.....	10	0	0	6	60	6	60	4	40
++.....	36	12	33	15	41	27	75	9	25
+.....	24	13	54	7	29	20	83	4	17
+*.....	30	10	33	10	33	10	66	10	33
Total.....	100		35		37		73		27

\* = Patients having a corrected sedimentation index within the normal range.

Ten of the patients studied had an advanced, active deforming type of arthritis and six of these showed moderate improvement. Thirty-six patients had severe pain and swelling of the joints and of these 12 showed marked improvement, 15, moderate improvement, while nine failed to respond to treatment. Twenty-four patients were treated who had severe pain and stiffness of the joints but no evidence of swelling at the time of examination and all but four showed improvement, 13 improving markedly, and seven moderately. Thirty patients had joint pains and stiffness similar to the above group but a corrected sedimentation rate within the normal range at the time of admission. Ten of these patients showed marked improvement, 10 moderate improvement, and 10 no improvement.

A patient was not considered improved unless there was a drop in the corrected sedimentation index, if previously elevated, as well as improvement in the clinical symptoms. In table 2 is shown the average corrected sedimentation index for the +++, ++, and + groups, before and after treatment, of the patients who improved as compared with those who failed to respond.

TABLE II

Effect of Treatment on the Corrected Sedimentation Index

Severity	Average Corrected Sedimentation Index			
	Patients Improved		Patients Unimproved	
	Before Treatment	After Treatment	Before Treatment	After Treatment
+++.....	1.43	0.92	1.28	1.38
++.....	1.18	0.71	0.90	1.03
+.....	0.73	0.45	0.91	*

\* = Two of the four patients in this group failed to return for a repeat test.



As might be expected, the average corrected sedimentation index was higher for the patients with more advanced arthritis. There were 10 in this group and the corrected sedimentation index before treatment ranged from 0.7 to 2.0, with seven having an index of 1.4 or higher. The corrected sedimentation rate for the patients with a moderately severe arthritis ranged from 0.5 to 1.6, with 80 per cent having an index of 1.0 or higher. For the patients showing a mild form of arthritis the corrected sedimentation index ranged from 0.4 to 1.4 with 75 per cent having an index of 1.0 or less. Following treatment there was a drop of five points in the average corrected sedimentation index for the patients showing improvement in the +++ and ++ groups and a drop of three points for the patients in the + group.

It was a matter of interest to compare the number of injections and duration of treatment of the patients who improved with those who did not. In treating ambulatory patients in a clinic it is difficult to control the number of visits. Many patients become discouraged and fail to return after a few visits. In table 3 is shown the average number of injections and average duration of treatment for the three groups of patients studied.

TABLE III  
Relationship of Number of Injections and Duration of Treatment to Improvement

Severity	Average Number of Injections		Average Duration of Treatments	
	Improved	Unimproved	Improved	Unimproved
			(Months)	
+++.....	31.5	18.5	5.6	2.6
++.....	21.5	15.5	4.5	2.5
+.....	18.7	13.7	3.8	1.9
+*.....	14.5	15.9	3.2	3.5

\* = Patients having a corrected sedimentation index within the normal range.

Of the 10 patients with advanced arthritis the number of injections for the six who improved was 8, 17, 27, 37, 48, and 52 respectively, with an average of 31.5, while the four who failed to improve had 9, 13, 24, and 28 injections, with an average of 18.5. The duration of treatment for the former varied from two to 14 months and for the latter, from two to four months.

For the patients with a moderately severe arthritis the range of injections was from nine to 48 with an average of 21.5 for those who improved, while it varied from six to 25 with an average of 15.5 for those who did not respond. In the improved group half of the patients received 20 or more injections, while only two of the nine patients in the unimproved group

received as many. The duration of treatment for the former varied from one to 12 months, while for the latter it varied from one to four months.

For the patients with a mild arthritis and an elevated corrected sedimentation rate the number of injections for those who improved varied from six to 38 with an average of 18.7 and the duration of treatment from one to 10 months; while for those who failed to respond it ranged from eight to 26 injections with an average of 13.7 and a duration of from one and a half to three months. For the patients with a mild arthritis and a normal corrected sedimentation rate the average number of injections was 14.5 with an average duration of 3.2 months for the improved group and 15.9 injections over a period of 3.5 months for the unimproved group.

Very few untoward reactions occurred from the injections. One patient who was given a much larger dose than on the previous visit developed a severe urticaria immediately after the injection. It cleared up rapidly following an injection of adrenalin. One patient was given three wheals in the left forearm at the third visit. Two of the wheals disappeared in a few hours but one became inflamed and a cellulitis developed in the left hand and wrist two days later which required hospitalization and surgical intervention. Cultures from the site of injection were negative. The patient was found to have a history of recurring attacks of hay fever. Following the reaction the patient had complete relief from the arthritic condition and was well one year later.

#### DISCUSSION

The highest percentage of improvement occurred in the group of patients having a mild form of arthritis but with an elevated corrected sedimentation rate. However, the patients with the same form of arthritis but having a normal corrected sedimentation index did not respond well to treatment. This is probably due to the fact that many of the latter group were old or quiescent cases and some may not have had a true rheumatoid arthritis. This type of patient does not respond well to any of the usual forms of therapy.

As might be expected, improvement was directly related to the duration of treatment. The patients who improved had injections on an average of two to three months longer than those who failed to respond. Like most forms of therapy for rheumatoid arthritis it was necessary to continue the injections over a long period of time to get the best results.

In giving bee venom in the form of *Apicosan* care must be exercised in order to avoid reactions. The dose should be increased slowly and the patient should be questioned at the next visit regarding redness, pain and swelling at the site of the injection. The test dose (0.1 c.c. of concentration N) should always be given preliminary to starting the treatments as some people are very sensitive to bee venom.

It is of interest to compare the results obtained in this study with those following the use of vaccine. In 1933 Stainsby and Nicholls<sup>7</sup> reported an improvement of 58.3 per cent in a group of 103 patients treated by the removal of diseased tonsils and injections of hemolytic streptococcus vaccine. One hundred and ninety-four patients in whom the focus of infection had been removed before coming to the clinic were treated with vaccine only and 35.9 per cent showed improvement.

#### SUMMARY

1. One hundred patients with rheumatoid arthritis were treated with an injectable form of bee venom (*Apicosan*) and 73 showed improvement. Thirty-five of the patients were markedly improved and 38 moderately improved. There was definite and lasting relief from the pain and swelling and a drop toward normal in the corrected sedimentation rate, if previously elevated.

2. The number of injections varied from 6 to 52 over a period of from one to 14 months. The patients who received on the average a longer course of treatment showed the greater improvement.

3. In estimating the results obtained from this study of an injectable form of bee venom (*Apicosan*) for rheumatoid arthritis one is impressed with the definite improvement in the clinical symptoms and the significant drop in the corrected sedimentation index in a large percentage of the patients. It would seem, therefore, that bee venom is worthy of further consideration.

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## MECHANISM OF THE TOXIC EFFECTS FROM COMBINED USE OF CALCIUM AND DIGITALIS \*

By J. S. GOLDEN, M.D., and WILLIAM A. BRAMS, M.D., *Chicago, Illinois*

THE administration of calcium with digitalis was considered a safe combination to enhance diuresis and to increase the effects of digitalis by Berliner,<sup>1</sup> Billigheimer<sup>2</sup> and Singer.<sup>15</sup> Recently, however, Bowers and Mengle<sup>4</sup> reported sudden death in two patients who received calcium intravenously after previous administration of digitalis, and similar results were noted in animals that received a similar combination. Available experimental evidence points to either a synergistic effect or an additive phenomenon as the underlying factor for such untoward results. Lloyd<sup>17</sup> reported the electrocardiographic changes observed on himself during intravenous administration of calcium chloride, using first 50 c.c. of a 1 per cent solution and then a 10 per cent solution. No significant changes were observed during injection of the weaker solution but subsequent use of the 10 per cent solution resulted in cardiac standstill after but 4 c.c. had been given. Complete recovery followed when the injection was stopped at that point but this experience shows that intravenous injection of calcium is not always harmless. Walters and Bowler<sup>16</sup> injected a 10 per cent solution of calcium chloride intravenously in dogs and found electrocardiographic evidence of changes in rate and conduction. Ventricular fibrillation was observed after toxic doses but therapeutic amounts resulted only in changes in heart rate. Billigheimer<sup>3</sup> explains the change in rate as due to an effect on the vagus. Lieberman<sup>9,10</sup> reported that intravenous injection of calcium produced effects closely resembling those produced by digitalis, namely, rise in blood pressure, slowing of the pulse, heart block, and various arrhythmias. This author<sup>10,11</sup> believes that intravenous calcium produces an almost instantaneous digitalis-like effect on the heart while an interval of time is required for digitalis to act. He thinks that the result of both drugs given simultaneously or shortly after one another is merely additive. Billigheimer<sup>2</sup> thinks that calcium and digitalis act on the same structures of the heart but believes that digitalis sensitizes this organ to calcium. Similar observations were made by Mandelstamm<sup>13</sup> and by Issekutz.<sup>8</sup> It is of interest to note that Edens and Huber<sup>6</sup> found the blood calcium to be elevated when bigeminy pulse appeared after digitalis and that Cushny<sup>5</sup> reported less complete cardiac contractions after digitalis when the calcium content of the perfusion fluid in his preparations was reduced. Fischer,<sup>7</sup> using isolated frogs' hearts, observed that calcium in the strength used in Ringer's solution, or in higher concentrations, had no effect if given before or during digitoxin administration but a marked calcium effect became apparent if

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digitoxin was employed before the calcium. He thinks that digitoxin sensitizes the heart to calcium but points out that this synergistic effect is one-sided, being effective only if digitoxin is given first. Schuntermann<sup>14</sup> found greatly increased amounts of calcium in portions of dried myocardium in instances of cardiac hypertrophy with failure.

These differences in opinion as to the safety of the combined use of calcium and digitalis prompted us to reexamine the question in order to study the various factors and underlying mechanisms which may be responsible for the untoward results or death following this procedure.

#### PROCEDURE

Eleven dogs, each 8 to 12.5 kilograms in weight and anesthetized with sodium barbital, were employed. Digalen \* was administered intravenously to the animals at a constant rate and in doses from 50 to 90 per cent of the calculated lethal dose (1.12 cat units per kilogram). After an interval of from 30 to 54 minutes 10 or 20 per cent solution of calcium gluconate was injected in the vein in five of these dogs. The quantity of calcium gluconate used did not exceed 20 per cent of the approximate lethal dose in any instance and the rate of injection was 4 c.c. or less per minute. Five other dogs received similar quantities of the two drugs simultaneously from the same syringe. The same precautions as to rate of injection and quantity of calcium were observed. Blood pressure variations were noted throughout each experiment. Electrocardiographic studies were made which included a three-lead control and repeated tracings of Lead II after each injection as well as prior to the death of the animal.

#### DISCUSSION AND RESULTS

The results are summarized in tables 1 and 2. In table 1 are shown the experiments where calcium gluconate was given 30 to 54 minutes after the digalen. The results obtained when the calcium gluconate and digalen

TABLE I

Experiment Number	Per Cent of Calculated Lethal Dose of Digalen	Calcium Gluconate	Time Interval	Result
1	85	15 c.c. 10%	30 min.	Immediate death
2	66	25 c.c. 10%	36 min.	Immediate death
3	60	11 c.c. 20%	54 min.	Dog destroyed after 22 min.
4	50	35 c.c. 10%	31 min.	Death in 60 min.
5	50	35 c.c. 10%	38 min.	Death in 90 min.

\* We are indebted for the supply of digalen to Dr. L. Klein of Hoffmann-LaRoche and to H. Althouse of Sandoz Chemical Works for the calcium gluconate employed in these experiments.

were given simultaneously are shown in table 2. It will be seen that death occurred in both types of experiment with less than the calculated lethal doses of digalen, indicating that the calcium gluconate was in some way responsible for the greater effectiveness of digalen. Neither the rate of injection of calcium, which was constant in all experiments, the concentration or the total dose, which was never more than 20 per cent of the calculated lethal dose, could be responsible for death in some of the animals. Death of the animals and the time lag of its occurrence were found to depend on (a) the amount of digalen given, and (b) on whether the calcium gluconate was given simultaneously or at a short interval after the digalen. Both tables show that death occurred earlier with larger doses of digalen. It was also observed that death occurred earlier and was more likely to be

TABLE II

Experiment Number	Per Cent of Calculated Lethal Dose of Digalen	Calcium Gluconate	Time Interval	Result
1	83	17.5 c.c. 20%	0	Death 17 min.
2	68	15 c.c. 20%	0	Living 28 min.
	17	15 c.c. 20%	28 min.	Death 2 min.
	Total 85			
3	66	17.5 c.c. 20%	0	Death 50.5 min.
4	50	17.5 c.c. 20%	0	Death 32 min.
5	50	17.5 c.c. 20%	0	Living at 107 min.
6	50	17.5 c.c. 20%	0	Living at 112 min.

(1) 0 equivalent to simultaneous administration.

(2) Dog 2 received a second dose of digalen (17 per cent of the calculated lethal dose) 28 minutes after the injection of calcium and showed no change for 28 minutes until another injection of calcium was given. Death then occurred in 2 minutes.

sudden with the same large dose of digalen if the calcium was injected about 30 minutes after the digalen. This, of course, is due to the time lag before the full action of digalen appears. In other words, in the simultaneous injections the calcium effect could have worn off considerably before the digitalis effect had become prominent. Nevertheless, it is significant that death sometimes occurred after a long interval when smaller doses of digalen were used. Apparently the effect of calcium gluconate may sometimes be more prolonged than is generally supposed.

The lag in death with smaller doses of digalen is in accord with some unreported results obtained by one of us (W. A. B.) with cats which indicated that intravenous injections of very large doses of digitalis resulted in toxic effects within a few minutes while comparatively small doses of digitalis required more time to produce comparable effects.

The present study indicates the hazard existing in the use of calcium gluconate intravenously following digitalis. Great caution should be used in patients who have received digitalis, especially if they show electrocardiographic or other evidence that they are digitalized. Even the simultaneous injection of calcium and digitalis in patients who have not previously received digitalis is not a harmless procedure. It is especially dangerous if larger doses of digitalis are given but untoward results may occur with smaller therapeutic doses. Our animal experiments suggest that the margin of safety in such combinations is both variable and narrow and that death may occur as late as one to one and one-half hours after injection.

Our experiments throw no light on whether death is due to additive phenomena or to a synergistic effect but it was observed that blood pressure rose shortly after injection of digalen in most instances to be followed by a precipitous drop before death after calcium was given. Electrocardiographic observations show the usual changes after large doses of digitalis, namely, changes in the T-wave and ST segment, heart block and ventricular tachycardia. Subsequent injection of calcium resulted in ventricular tachycardia and ventricular fibrillation. The latter mechanism was the cause of death in the animals who died immediately as well as in those who lived for as long as 90 minutes. Even those who survived developed ventricular tachycardia when digalen and calcium were injected simultaneously.

#### RÉSUMÉ

1. A series of experiments was performed to study the dangers and their mechanisms, inherent in administration of calcium with or shortly after digitalis.

2. We are in accord with previous observers who noted marked toxic effects or death when such combinations were used. These results could not be attributed to the digalen alone nor to the concentration, dose or rate of injection of the calcium.

3. The toxic or fatal effects depended on the size of the previous dose of digalen and depended a great deal on the time interval between injection of digalen and calcium. Toxic manifestations and death occurred when larger doses of digalen were used. These were more likely to occur if calcium was injected about 30 minutes after the digalen.

4. It was also observed that the margin of safety was narrow and uncertain and that the toxic effects following calcium, when digalen was given before, resembled those seen after very large doses of digitalis alone. Simultaneous injection of both drugs in similar dosage was somewhat less toxic and was less likely to be fatal than when an interval of about 30 minutes elapsed between the injection of digitalis and calcium.

5. Death in our animals was associated with a precipitous fall in blood pressure, and electrocardiograms revealed that ventricular tachycardia was frequent and that death was due to ventricular fibrillation.

6. The conclusion is reached that great caution is to be used in giving calcium intravenously with or shortly after digitalis. It is apparently not safe to use this combination even in patients who have received small doses of digitalis, but it is particularly dangerous if there is electrocardiographic or other evidence that the patient is approaching digitalization. We believe that it is wiser to abstain from intravenous injection of calcium in any patient who is receiving digitalis since the margin of safety is so narrow and the toxic effects can neither be foreseen nor successfully treated.

We are indebted to Messrs. A. C. Meyer, Jr., and R. Blake for technical assistance in these experiments.

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# THE PRESENT STATUS OF RHEUMATISM AND ARTHRITIS: REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1936 \*

(Fourth Rheumatism Review)

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† Dr. Ghrist died February 3, 1937.

Common types of spondylitis: atrophic; hypertrophic  
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#### GENERAL INCIDENCE OF RHEUMATIC DISEASES; SOCIAL AND ECONOMIC IMPORTANCE

STATISTICS again demonstrate that the rheumatic diseases represent one of the world's greatest social and economic problems. Of all patients admitted in 1933 to accredited hospitals in the United States, 97,984 patients (1.39 per cent) were admitted because of "arthritis or rheumatic diseases" (Kling<sup>313</sup>). A recent Public Health Survey (Collins<sup>98</sup>) calculated the incidence of "chronic arthritis and rheumatic diseases" as 22.18 per 1000 persons, or 2.2 per cent of the population of which more than 1 per cent had "disabling" rheumatism and 0.85 per cent were "bedridden." (The morbidity rate for tuberculosis of all forms, including suspected cases, was only 4.72 per 1000, about one-fifth that of chronic rheumatism.) Based on these figures, Kling calculated that about 2,700,000 of the 120,000,000 population in the United States are affected with chronic rheumatic diseases, of whom 1,230,000 are "disabled" and 1,020,000 have been bedridden at some time or other. (Presumably the remaining 450,000 persons were affected mildly or moderately, not seriously enough to be "disabled" or bedridden.—Ed.) Kling believes this to be a low estimate. According to the Massachusetts survey (1933),<sup>245</sup> 3,264,000 persons or 3.2 per cent of the population of the United States suffer from chronic rheumatism.

The incidence of joint diseases in Finland is evidently less. In a house-to-house canvass of 37 rural communities with a population of 195,000 persons, Holsti and Rantasalo found 1702 persons (0.9 per cent) who had suffered or were suffering with "acute or chronic joint disease"; of these 1177 had chronic arthritis, 525 had acute arthritis. Sex incidence of those affected was 2.4 females to 1 male; in acute cases 1.7:1, in chronic cases 2.7:1. The incidence of arthritis in different localities varied greatly from 0.3 to 4.3 per cent of the population, and was highest in southeastern Finland, on the coast of Lake Laakokka, where endemic struma is common.

#### CLASSIFICATIONS OF DISEASES OF JOINTS AND RELATED STRUCTURES

The editors of these reviews<sup>245, 246, 247</sup> sympathize with Haden when he stated, "It is hopeless to discuss the different classifications or the different terms used to indicate the same clinical type of pathologic process." In the third review we therefore dismissed the year's crop of "new classifica-

tions" briefly since none seemed subject to less criticism than those in common use. A commission of the International League against Rheumatism has already collected more than 60 different nomenclatures. The ultimate classification of "rheumatic diseases" will be one based on a complete understanding of the etiology of the different forms. Until an etiologic classification can be completed it is necessary to use working classifications based on clinical data, pathologic or roentgenographic features or combinations thereof. None is entirely satisfactory but some have more merit than others. Because of the fundamental differences of opinion among the various schools of thought it is difficult to set up a nomenclature universally acceptable. But to avoid clinical confusions and for statistical purposes an international classification would be most helpful. To foster such a classification the International League against Rheumatism has asked committees in each country to simplify its own nomenclature to bring out the essential features of each disease-type. Coöperating in this work, a committee appointed by the American Rheumatism Association is critically reviewing major classifications now in use. This review will therefore not include critical comments on new ones proposed. Those interested in suggestions, amendments and criticisms of classifications in current use may consult the following references: 4, 14, 129, 177, 183, 191, 228, 286, 368, 428, 476

#### DISEASES OF JOINTS RELATED TO TRAUMA

Trauma is related to articular disease in three ways: it may be the chief or sole cause of "pure traumatic arthritis"; it may precipitate various types of arthritis, chief cause of which is some factor other than trauma; it may aggravate a preëxisting active or quiescent nontraumatic arthritis. Campbell regards traumatic arthritis as the commonest type of joint affection.

(This may be true in the practice of an industrial surgeon or orthopedist but is not the experience of most physicians unless one regards as traumatic arthritis all three of the relationships listed.—Ed.)

*Articular Diseases Due Primarily to Trauma.* Three types of trauma produce articular damage<sup>76</sup>: (a) A single mild or severe injury which damages articular structures with varying degrees of severity; (b) repeated occupational trauma from overuse and excessive wear and tear of joints; (c) repeated "microtrauma" from faulty posture or attitudes producing functional disability from unevenly distributed intra-articular pressure.

*Symptoms.* The usual symptoms of pure traumatic arthritis result from the reaction of synovial, capsular or articular tissues to the irritative process.<sup>76</sup> Traumatic arthritis is usually monarticular; rarely bilateral or polyarticular. Pain and slight swelling are generally present. Periarticular skin temperature, often increased in infectious arthritis, is usually normal in traumatic arthritis. On motion, crepitus may be present from a thickened capsule, synovial villi, or irregular articular surfaces. The joint may appear normal or effusion may occur. Large effusions may force articular

structures to assume abnormal positions which provoke muscle spasm and limited motion.

*Pathology.* Chief lesions produced are cartilage degeneration and, less notably, synovial fibrosis. There is early splitting of the cartilage matrix and subsequent fibrillation which may result in complete destruction of the cartilage of weight-bearing surfaces or of cartilage covering those surfaces affected by trauma (Ghormley and Deacon). These changes result because cartilage has little reparative powers. Marginal osteophytes appear later. The development of these changes has been reviewed (Campbell, Kling). Synovial hydrops is followed by formation of fibrin which may become organized into fibrous tissue adhesions. Synovial villi may increase in size and number. Beneath the synovia a fibrous tissue reaction occurs. Disease of cartilage produces no pain as sensory nerves are absent. When significant intra-articular hemorrhage occurs the synovia responds by hypersecretion, becomes thickened and inflamed. Blood is broken down; fibrin is precipitated and becomes organized with formation of adhesions.

*Roentgenogram.* In the early stage of traumatic arthritis roentgenograms may be normal or may reveal subchondral osteoporosis. Later the hypertrophic changes and osteophytes are seen.

*Synovial Cytology and Chemistry.* Normal synovial fluid contains about 10 to 200 nucleated cells per cu. mm., and, according to Collins, a small, variable number of erythrocytes, from the trauma of aspiration. Only an occasional polymorphonuclear leukocyte occurs among the nucleated cells, 90 to 95 per cent of which are phagocytic cells resembling either monocytes of blood or macrophages of probable connective tissue origin. Collins studied the cytology of five traumatic effusions between seven and 51 days after injury. Variations in total and differential cell counts were as follows: erythrocytes, 200 to 25,000 per cu. mm.; total nucleated cells, 150 to 856 per cu. mm.; polymorphonuclears 2 to 32 per cent, lymphocytes 34 to 77 per cent, monocytes 9 to 18 per cent, macrophages 0 to 8 per cent, synovial cells 3 to 38 per cent.

In hemorrhagic traumatic effusions Kling found an increase of mucin, the presence of which increases the viscosity of the effusion. As a result of hemorrhage, the bilirubin content of the effusions may be increased for as long as six weeks after an injury. The icteric index of traumatic effusions is above 5, that of inflammatory effusions is invariably below 5. Other than trauma, only a few conditions (hemophilia, tabetic atrophy, xanthoma, sarcoma) cause spontaneous intra-articular bleeding and a high bilirubin content in effusions. The presence of fat in traumatic effusions distinguishes severe injuries from simple tears of joint capsule. If the fat is chiefly palmitin and stearin, it presumably originates from fat torn loose from fat pads and may indicate an injury to the intra-articular cartilages or to ligaments. If it is chiefly olein it must come from bone marrow; therefore its presence indicates intra-articular fracture. In such cases bone marrow cells may also be present in effusions.



## SPECIAL FEATURES AND VARIETIES OF TRAUMATIC DISEASE OF JOINTS

1. "*Post-Traumatic Bone Atrophy*"; "*Post-Traumatic Periarticular Fibrosis*." In 1900 Sudeck described an "acute post-traumatic inflammatory atrophy of bone." Since then considerable attention has been paid to the osteoporosis, but little to the associated periarticular fibrosis. The cause of this osteoporosis is unknown but is presumably the result of a physiologic process which follows every toxic or traumatic irritation and is probably the result of an increased circulation to the part from vasomotor alterations initiated by the sympathetic nervous system. Absorption of bone salts appears in roentgenograms as a "spotty atrophy" or mottling.<sup>76</sup> It is differentiated from the atrophy of disuse, which is characterized by gradual encroachment of the marrow on the cortex and by diminution in the size of the entire bone.

Post-traumatic bone atrophy may be painful. In one case Ghormley noted atrophy of cartilage. Gordon regarded the bone atrophy as secondary to the earlier periarticular fibrosis. Following an injury or fracture of an extremity, swelling and a soft pitting edema distal to the lesion may appear and persist. Joints of hands or feet may become painful and stiff due to proliferation of periarticular fibrous connective tissue. Subsequent decalcification of bone occurs. Lymph stasis supervenes; later the vascular content of subcutaneous tissues is apparently reduced. Overgrowth of periarticular connective tissues occurs; limitation of motion and pain are present, contractures and protective muscle spasms ensue, and atrophy results. In severe cases roentgenograms show decalcification of bone, slight thickening of periarticular tissues, narrowing of joint spaces. If the original injury or fracture is near the torso, this condition is less likely to affect hands and feet because collateral circulation of blood and lymph distal to the original injury is generally adequate.

The condition is avoided by preventing or correcting capillary and lymph stasis. Only that part of the extremity for which rest is vital should be kept at rest. Rings should be removed. Dressings should not be constrictive. Adequate, protective cotton pads should be used with splints and the latter should be temporarily removed to permit massage if swelling appears. Frequent elevation of affected extremities is important. Usually the condition clears satisfactorily; occasionally it is protracted. In severe cases one or two toes or fingers may become ankylosed. Relief was obtained in two cases treated by White with procaine injections of sympathetic ganglions.

Apropos of these statements is Jones' interesting review of the conditions which foster articular adhesions with injury or disease.

The following questions were raised and answered by Jones: Why may joints sometimes be immobilized without becoming stiff, whereas at other times dense adhesions form although joints have not been completely immobilized? Why can some joints be immobilized for a year with impunity, and others become permanently stiff within a few weeks? Why is the wrist joint more likely to become stiff when immobilized in a cock-up splint and not in a dorsal plaster splint? Why do massage

and passive stretching always aggravate stiffness of finger and elbow joints? Joint adhesions from injury are generally formed, not in intra-articular or interarticular, but in periarticular, tissues. Stiffness results from periarticular adhesions in the plications of joint capsule. Adhesions arise from organization of periarticular sero-fibrinous exudate which provides the adhesive substance responsible for the gumming together of adjacent tissues. First a fibrinous deposit occurs, later fibrin is replaced by young connective tissue, ultimately by fully formed fibrous tissue. When traumatic (or infectious) synovitis occurs, or when the joint capsule is torn, exudate is poured out from synovia or from torn edges of the capsule. Even though the joint is normal, periarticular adhesions may form as a result of certain extra-articular conditions: a spreading exudate from distant injury or infection, recurrent edema of juxta-articular tissues, simple venous stasis and congestion due to muscular inactivity of immobility and disuse. The potency of these factors in promoting adhesion formation depends on the degree of exudation, the fibrin content of the exudate and the frequency with which the soaking is repeated. The recurrence and persistence of serofibrinous exudation provide the key to adhesion formation. If articular tissues are soaked in exudate, day by day, adhesions will form whether immobility is complete or incomplete and whether the joint is injured or normal. If injury is not repeated, even a severe fracture of an elbow joint will cause less adhesion formation than the relatively trivial injury of passive stretching repeated day after day by an overenthusiastic masseur. Adhesions form less readily about an ankle joint immobilized in a walking plaster cast than about the same joint left free to move but subject to recurrent edema. "Edema is the glue from which adhesions are made." (Not ordinary edema, but that from inflammation and trauma.—Ed.)

2. *Pellegrini-Stieda Syndrome*. When the medial collateral tibial ligament of a knee is traumatized a peculiar reaction may occur therein: bone may be formed in the ligament. This is the Pellegrini-Stieda syndrome, recently described in American literature (Kulowski, 1933). Two cases were reported (Henson). Each involved a history of recurrent trauma, swelling of the knee and pain on motion. Roentgenograms revealed the condition. Surgical procedures used in treatment were outlined.

3. *Tennis-Elbow*. There is no unanimity of opinion concerning the basic pathology or the optimal treatment of "tennis-elbow." According to Cyriax, it is caused primarily by a tear between the tendinous origin of the *extensor carpi radialis brevis* and the periosteum on the anterior surface of the lateral epicondyle; a chronic periostitis results secondarily and to this symptoms are referable. Cyriax described his method of treatment which gave "complete and lasting relief": repeated deep friction to the tender area, followed by forced adduction of the extended and supinated forearm.

*Medicolegal Aspects of Traumatic Arthritis*. Data considered necessary by some to determine the presence of traumatic arthritis and to assess the degree of disability therefrom have been given.<sup>245, 247</sup> It was stated that, in addition to other data, one should have information on the time between injury and onset of symptoms; it should not be more than a few months to a year. Some disagree on this last point. According to Henry the injury must be severe enough to cause immediate cessation from work and symptoms must appear immediately (or within a few days) after the accident and persist continuously. According to Lecklitner "bridge symptoms"

must be present, that is, the symptoms (to be caused by traumatic arthritis) must have continued uninterruptedly from the time of trauma to the onset of arthritis, and other joints of the body must be free of arthritic lesions.

*Nontraumatic Arthritis Precipitated by Trauma.* Mild trauma may instigate or precipitate an arthritis (atrophic or tuberculous, or that from syphilis, pyogenic infections or neoplasms) the chief cause of which is some factor other than trauma. In a gouty patient mild trauma may initiate a severe attack of gouty arthritis, out of all proportion to the degree of trauma which provoked it (Campbell, Kling).

*Nontraumatic Arthritis Aggravated by Trauma.* Any preëxisting arthritis (most commonly hypertrophic, senescent or degenerative osteoarthritis) may be aggravated by trauma. In patients with previously asymptomatic, senescent hypertrophic arthritis trauma may induce persistent symptoms. In such cases the medicolegal question arises: how much disability is attributable to trauma and how much to the previously existing disease? <sup>76</sup>

In three patients Epstein noted results of severe trauma to joints ankylosed from previous disease. Fracture occurred not at the site of ankylosis but in adjacent, thinner para-articular bone. Hence a completely welded, eburnated articulation of two long bones of an extremity, that is, a true ankylosis, is a mass of bone of greater strength than that of nearby "healthy" bone.

#### TREATMENT OF TRAUMATIC ARTHRITIS

Current treatments are as previously outlined in the first three reviews. Aspiration of traumatic effusion evacuates pathologic products from joint cavities and reduces inflammation (Kling). Henson inflated joint cavities with oxygen to prevent and to "break up" post-traumatic adhesions (also those from infection). Weight bearing and physiotherapy were used in addition to oxygen inflations. Motion of joints was restored more readily and more painlessly by this combination than otherwise. Pain was generally decreased and manipulation of joints avoided.

Histamine ionization was advocated (Mackenna). Short wave therapy was used by Speeding.

(Evidence proving the superiority of these measures was almost wholly lacking in these reports.—Ed.)

#### "GONORRHEAL RHEUMATISM": GONORRHEAL ARTHRITIS

*Incidence.* In the United States 700,000 persons apply annually for the treatment of acute gonorrhea (Barney). According to Usilton (1935) about 500,000 patients in the United States are constantly under treatment or observation for gonorrhea. Considering those with gonorrhea who never report for treatment it has been estimated that between 1,000,000 and

2,000,000 new infections with gonorrhea occur yearly in this country (Thomas and Bayne-Jones; Barney). About 3 to 5 per cent of persons with gonorrhea are said to develop gonorrheal arthritis of varying severity. A much lower incidence is reported from Johannesburg, South Africa: of 6000 patients with gonorrhea, 30 (0.5 per cent) developed gonorrheal rheumatism (Bayer).

*Clinical Features.* Reviewing the clinical features of gonorrheal arthritis Warren stressed certain points. A careful history usually reveals transitory involvement of many joints for several days at the onset, then the acute major involvement, generally of one but not infrequently of several joints or near-by structures. Often the process subsides in one joint and flares up successively in other joints, particularly in a previously traumatized joint. In some cases the process is restricted entirely to tendon sheaths or bursae around a joint or to nearby muscles and fascia. A notable feature is the rapidity with which the acute arthritis and bone and muscle atrophy progress.

Gonorrheal arthritis in children is rare. In one series of cases it occurred in 1.5 per cent of children with gonorrheal vulvovaginitis (Gittings and Mitchell, 1917). Su and Hu noted severe gonorrheal polyarthritis in a girl aged four years who had apparently contracted the disease from recently infected parents. The child developed vulvovaginitis, fever, adenopathy and arthritis in three joints. Although treatment was chiefly symptomatic, articular recovery was complete.

(It often is if organisms do not invade the articular cavity.—Ed.)

The simultaneous occurrence of gonorrheal arthritis in a mother and a newborn infant is rare; an instance is reported by MacLennan. Infants with gonorrheal ophthalmia may develop arthritis between the fifth day and the fifth week, generally the second week, of infection. Although infants with severe ophthalmia may die, prognosis regarding joints is usually good.

Most cases of persistent gonococcemia are fatal. Among the 27 cases of nonfatal gonococcal septicemia without endocarditis reported in the literature two patients had erythema nodosum. An additional case was reported by Bakst, Foley and Lamb.

*Pathology.* The "classical type" of reaction occurs when articular tissues are directly invaded by gonococci. There is an inflammatory synovial reaction with infiltration of leukocytes, lymphocytes and macrophages. In synovial exudates are found gonococci and inflammatory cells, especially leukocytes. Jordan regarded as unproved the existence of a "second type" of gonorrheal arthritis in which gonococci are not found in articular and peri-articular tissues to explain the inflammation therein. Some suppose that such a type represents an "allergic gonorrheal arthritis," a sensitization of joint tissues to metabolic products of distant gonococci. According to Ghormley and Deacon, the pathologic reaction in gonorrheal arthritis is essentially similar to that of other pyogenic forms of arthritis: synovial

thickening, edema, polymorphonuclear leukocytic infiltration; later the production of fibroblasts and capillaries, infiltration by plasma cells and polymorphonuclear leukocytes, and still later the advanced stage of synovial fibrosis. Differences in reaction depend largely on the number and virulence of the organism and the patient's resistance.

*Roentgenograms.* In acute gonorrheal arthritis roentgenograms present no special characteristic except perhaps the early and unusual, diffuse character of the atrophy and the marked, often rapid, bone destruction (Warren). Taylor and his colleagues regarded this feature as of considerable diagnostic value to clinicians. The appearance of a gonorrheal joint of six weeks' duration may closely resemble the appearance of a joint with tuberculous involvement of six months' duration. To suggest a diagnosis of gonorrheal arthritis, therefore, a roentgenologist should know at least the duration and severity of articular symptoms. Studying roentgenograms in 11 cases, Taylor and associates noted marked variations at different stages of the disease. In the "early stage" marked soft tissue swelling appeared early and subsided within a few days or weeks. Local areas of decalcification and slight effusion were each noted in 64 per cent of these cases. Later these both decreased. Later still there was narrowing of joint spaces in 82 per cent, a moderate degree of "active bone destruction" in 36 per cent, early healing with fibrous or bony ankylosis in 45 per cent.

*Laboratory Data.* A certified diagnosis of gonorrheal arthritis can be made only on recovery of gonococci from articular tissues or fluid. This is generally not done. A reasonably accurate presumptive diagnosis of gonorrheal arthritis is usually made on the basis of certain clinical data supported by laboratory evidence of the presence of urogenital gonorrhea. The elaborate report by Thomas and Bayne-Jones of the Committee for a Survey of Research on the Gonococcus and Gonococcal Infections contained much data of interest to clinicians: data on the biology of gonococci, on types of gonococcal infections, on the relative value of different methods of treatment of gonorrhea and on the respective merits of laboratory tests used in diagnosis.

1. *Isolation of Gonococci in Smears and Cultures.* Although in most cases of acute gonorrhea in males a diagnosis based on examinations of stained smears from secretions is probably correct, such a diagnosis is not free from uncertainty. Recent literature reflects a growing sentiment against relying on smears alone for diagnosis (Thomas and Bayne-Jones). Although opinions differ as to the relative value of smears or cultures for isolating gonococci, most workers now favor cultures. Warren's experience indicated that smears from urogenital discharges may be positive for gonococci in 40 per cent, cultures of such discharges may be positive in 60 per cent, and cultures of articular tissues may be positive in 80 per cent of cases in which gonorrhea is suspected. These percentages are higher than those of others. Leahy and Carpenter found the diagnostic value of smears slightly greater than that of older cultural methods but when they used a modification of McLeod's new (1928-1934) method the reverse was true. Ten per cent more positive cases of gonococcal infections were discovered by the new cultural method than by the smear method alone. Smears were positive in 45 per cent, cultures positive in 55 per cent of cases studied; in 13 per cent cultures were positive when smears were negative or doubtful; in 2



per cent cultures were negative but smears were positive. Similar results were obtained by Spohr and Landy, using another modification of McLeod's method. A study of material from male urethras gave the following results: Smears and cultures were both negative in 22 per cent of cases examined; smears were negative but cultures were positive in 10.3 per cent; smears were positive but cultures were negative in 7.7 per cent; both smears and cultures were positive in 60 per cent. The superiority of the cultural method was more notable in tests on material from suspected females. In studies of urethral secretions smears and cultures were both negative in 52.5 per cent; smears were negative but cultures were positive in 10.2 per cent; in no case were smears positive and cultures negative; in 37.3 per cent both smears and cultures were positive. Studies of cervical secretions revealed negative smears and cultures in 49.2 per cent; negative smears and positive cultures in 32 per cent; positive smears and negative cultures in none; positive smears and cultures in 18.6 per cent. Thus, in the latter group smears were positive in 18.6 per cent but cultures were positive in 50.8 per cent.

2. *Gonococcal Complement-Fixation Test.* Further experiences with this test indicated that, properly interpreted, it is of diagnostic value. For the test to be positive, enough antigen must be absorbed to stimulate the formation of sufficient antibodies to produce the reaction in blood and a period of time sufficient for the development of the reaction must have elapsed. In mild or subacute (as contrasted with acute) cases, or in those in which discharges are open and draining freely, and in which but little antigen is absorbed, the test may remain negative despite the presence of definite gonorrhea. The current reports of Warren, Pelouze, McEwen, Alexander and Bunim, Hirshland and Hirshland and Lin have restated the characteristics of the test: 1. The test may be negative the first two to six weeks of infection. 2. It may require 4 to 20 weeks for complete fixation to occur. 3. Tests should be repeated, especially if the first ones are negative. A positive test was frequently not obtained by McEwen and associates until the third bleeding. 4. Some <sup>265</sup> regard a repeatedly weak-positive reaction as specific as a (single) strongly positive reaction. (Others do not agree to this.—Ed.) 5. The test is more frequently positive in acute systemic infections (such as gonorrheal arthritis) or in chronic infections than in acute local infections. 6. Repeatedly negative tests are strong presumptive evidence against the presence of gonorrhea. 7. After patients have clinically recovered the test may remain positive for many months (as long as four years—Warren); therefore it is of little value as an immediate proof of cure. 8. The test generally becomes negative within 6 to 18 months after clinical recovery. 9. A persistently and markedly positive reaction in a case of presumed arrested gonorrhea strongly suggests the presence of a (hidden) active gonococcal focus.<sup>344</sup>

Results of the test confirmed the clinical diagnosis in 76.4 per cent of the cases of Hirshland and Hirshland who found it particularly useful in females from whom it is difficult to obtain positive pelvic smears. Of 44 patients with gonorrheal arthritis seen by McEwen, Alexander and Bunim, 98 per cent gave a positive reaction: 4 plus in 20 per cent, 3 plus in 33 per cent, 2 plus in 36 per cent, 1 plus in 2 per cent, doubtfully positive in 7 per cent. False positive reactions were found in no normal controls but in several pathologic controls: in 2 per cent of 48 cases of osteoarthritis; in 3 per cent of 39 cases of atrophic; in 3 per cent of 36 cases of miscellaneous arthritides; in 7 per cent of 70 cases of rheumatic fever. Some of the latter patients had rheumatic polyarthritis and coincidental urogenital gonorrhea.

Lin tested the sera of 500 persons, 323 with active or arrested gonorrhea and 177 with nongonococcal infections used as controls. Of the control cases 3 per cent gave false-positive reactions. The reaction was falsely negative in 25 per cent of the cases of gonorrhea proved active by smears. Of 187 specimens representing cases of active gonorrhea, smears and serologic reactions were both positive in 95 cases; smears alone were positive in 31 cases; the serologic reactions alone were

positive in 33 cases. Complement-fixation tests generally became negative in less than 6 months after patients were clinically cured.

According to Thomas and Bayne-Jones the present status of the test is as follows: In spite of technical improvements it still remains one which cannot be satisfactorily done by a poorly trained or indifferent technician, and is one which exhibits, even when skillfully performed, vagaries whose conquest will demand time and research. Variations of materials and procedures used for the test have been so numerous that they defy classification. Various antigens, solutions, autolysates and protein-fractions of the organism are used. A greater standardization of technic is necessary and the most reliable antigen must be found. Despite all this the weight of evidence conclusively shows the specificity and considerable diagnostic value of the reaction.

Koopman and Falker devised a "more sensitive and quantitative" method for the test, one which does not give false-positive or indefinite reactions except in cases of meningitis. (No results with the test were tabulated.—Ed.)

3. *Skin Tests.* Although some workers regard skin tests with various products of gonococci as of diagnostic value, there is no general agreement on their worth.<sup>543</sup> Conrad used the Corbus-Ferry filtrate and a control solution for skin tests on 50 cases with no history of gonorrhea, and on 50 cases with clinical and laboratory evidence of gonorrhea. Forty-eight hours after injection, 98 per cent of the 50 gonorrheal cases demonstrated a skin reaction averaging 2.3 cm. as compared to reactions averaging 0.2 cm. in the control cases. No false-positive or negative reactions were noted. According to Corbus, the mechanism of skin reactions to the Corbus-Ferry filtrate is due to allergy.

4. *Synovial Cytology.* The cytology of 5 specimens of synovial fluid in 2 cases of gonorrheal arthritis of "considerable chronicity" was noted by Collins. Total nucleated cells varied between 5,200 and 23,400 per cu. mm.; polymorphonuclear leukocytes, between 30 and 77 per cent.

*Treatment.* This includes the management of the primary focus, that of the infected joints, and general treatment. Although fever therapy is being more widely used to heal both the local genital and articular disease, older methods are used by many. Stressed were the importance of early treatment even in mild cases, bodily rest to prevent systemic invasion, strict avoidance of trauma to genital tissues from the over strenuous use of instruments, massage and strong chemicals, avoidance of sexual and alcoholic stimulation, and the choice of various urinary sedatives and urethral medicaments.<sup>26, 80, 100, 402, 420, 543</sup>

Local applications of different chemicals and the use of vaccines found little favor with Thomas and Bayne-Jones. When chemicals are strong enough to affect bacteria they generally irritate tissues. Most specialists in the United States question the usefulness of vaccines except perhaps in chronic or complicated cases. The manifold preparations made from gonococci and used as vaccines "indicate that none fulfills all requirements. After all in the present state of knowledge concerning the clinical composition of the organism and its metabolic products preparing them is like shooting in the dark."<sup>543</sup> Several, however, favored the use of Corbus-Ferry filtrate. With it James "cured" 20 of 34 cases and Jamieson "cured" all of 9 cases of acute or chronic gonorrhea.

(Data on controls were not given.—Ed.)

Corbus believed that the filtrate prevented complications; they occurred in only 3 per cent of 175 cases; arthritis never developed. In cases treated otherwise, when arthritis appeared it frequently yielded "completely in an exceedingly short time" with the use of filtrate and prostatic massage.

Others consider the filtrate valueless. The results of McKenna, Goldfader and Fishberg in the treatment of 34 cases of gonorrhea with routine treatment plus the filtrate were no better than those treated only routinely. Complications were not prevented. Spence obtained "uniformly poor results." Miller's<sup>367</sup> results with filtrate were "not remarkably better" than those obtained otherwise. Deakin's patients with acute gonorrhea did not do so well with the filtrate as without.

Bertoloty and Herraiz considered Loeser's (1930) method of producing active immunization by injections of live gonococci superior to classical vaccine therapy.

The treatment of the joints includes rest with the appropriate type and amount of immobilization, physiotherapy and analgesics. According to Hamilton, amiodoxyl (ammonium o-iodoxybenzoate) has a profound effect on the pains of gonorrheal arthritis although it is useless in atrophic or hypertrophic arthritis. He compared results in 38 patients with gonorrheal arthritis treated therewith to those in 30 patients treated with ordinary methods. Amiodoxyl relieved pain, shortened the period of disability and reduced the percentage of permanent disability more effectively than any other generally used treatment. Of those treated with amiodoxyl, 69 per cent were "cured," 18 per cent improved, 13 per cent unimproved. Of the control group only 7 per cent were cured; 37 per cent were improved and 56 per cent unimproved. (Results in the controls were worse than usually reported.—Ed.) The drug, given intravenously, may produce toxic manifestations, fever, erythema, vomiting, diarrhea, headache; when these occur its use should be promptly and finally discontinued or there may be a fatal result. Death occurred in one of Hamilton's cases and in five others noted in the literature.

(The reader cannot form an independent opinion from Hamilton's papers. Only meager details of his cases were given. His charts were difficult to interpret. The control group was apparently not comparable to that treated with the drug; 20 of the 30 control cases were of chronic, only 10 were of acute, arthritis. The analysis of the control group was "very incomplete because of lack of chart data." The value of the drug remains to be proved. It must be remembered that many cases of "gonorrheal arthritis" represent a transient polyarthralgia and disappear spontaneously.—Ed.)

Gold therapy was used by Slot and by Oren.

Aspiration, drainage and irrigation of joints were advised in severe cases.<sup>231, 238, 297</sup> Aspiration may relieve pain, protect intra-articular tissues from material which would destroy cartilage, prevent undue capsular stretching and reduce the formation of adhesions. If a large joint is involved and aspiration of synovial fluid reveals much fibrin, marked synovial leuko-

cytosis (more than 40,000 leukocytes per cu. mm.) and gonococci, Keefer favors irrigation through a small incision in the capsule. Burman devised an aspirating syringe with a side-cock adapter for injecting air into gonorrheal (and other) joints with effusion. Restorative treatment for joints includes the use of physiotherapy, protection of arches weakened by long rest, and procedures to correct flexion deformities or ankylosis.

For general debility blood transfusions and a liberal food intake were advised.<sup>297</sup>

*Fever Therapy.* None of those advocating the measures just described apparently used fever therapy or compared its results with those of other methods. The parade of experience with fever therapy has continued to provide further evidence of its superiority over other methods.

Bierman and Levenson noted further results of systemic heating plus additional focal heating. The patients' temperatures were first elevated by means of a hot bath and cradle of lights to about 105° F. (rectal). Then the pelvic temperature was further elevated to about 111° F. by pelvic (rectal or vaginal) diathermy electrodes. Sixteen patients with gonorrheal arthritis were given two to six fever treatments, each three to five hours in duration, about twice weekly. The previous duration of gonorrhea was 4 to 28 (av. 12.8) weeks; of the arthritis, 3 to 25 (av. 10.2) weeks. Most of the patients had previously been treated ineffectively by other measures. Two already had ankylosis. Complete restitution of articular function was obtained in 13 of the 16 patients, partial restoration in one and very little in the two with ankylosis. Bierman also reported excellent results in the treatment of 52 cases of gonorrhea in females, in 26 of which salpingitis was present. In 45 of the 52 cases the cervix and urethra were sterilized after an average of 2.4 treatments per patient; 15 of the 45 patients required only one treatment.

Stecher and Solomon considered fever therapy practical, safe and satisfactory in the hands of experienced attendants. It provided cure or marked relief in a high percentage of cases and saved much time from disability. Fifty cases of gonorrheal arthritis were treated in the Kettering hypertherm, generally at 107° F. for five hours<sup>516</sup>; 54 per cent were "relieved of all joint symptoms," 22 per cent were benefited and 26 per cent were not helped. Of the 50 cases, 41 were of acute arthritis (10 weeks' duration or less); nine were of chronic arthritis. Complicating conjunctivitis and iritis were promptly cured. Genital infections were generally but not always entirely cured.

Slaughter and Trautman, and Trautman with a Kettering hypertherm treated 25 patients with acute gonorrheal arthritis: 16 "recovered completely," five improved markedly, four moderately. Fifteen patients with chronic gonorrheal arthritis were also treated: ten recovered completely, three were markedly improved and two were not improved. Genital infections were cured concurrently in 22 of the 25 acute cases, in 14 of the 15 chronic cases.



Twenty-nine of Simpson's 31 patients with acute arthritis (of less than eight weeks' duration) and seven of 14 patients with chronic arthritis recovered "complete joint function." Marked articular stiffness persisted in two chronic cases in spite of fever therapy but was relieved by orthopedic manipulation under anesthesia followed at once by fever therapy. Urogenital infections were completely cured in 38 of the 45 cases, soon disappeared spontaneously in four others, but two patients who had insufficient fever needed additional treatment.

Of McClure's 16 patients with acute or chronic gonorrheal arthritis, nine were "cured," four improved, three stopped treatment prematurely. "In some instances there was complete or almost complete relief from symptoms following the first treatment and from the experiences with these patients it is very definitely felt that fever therapy alone is often sufficient to effect a complete cure." For chronic cases supplementary physiotherapy was advised.

Using a "hot box" alone Gurnee cured only 55 per cent of his cases of gonorrhea in females. Treatments were strenuous and unsatisfactory. Thereafter patients were treated in the "hot box" with additional pelvic heating by the Elliott method, oral temperatures being kept at 105° F.; the water in the vaginal bag was at 115 to 118° F. Thus, higher rectal temperatures were obtained in the presence of moderate cerebral temperatures and heat stroke was avoided. All of five cases of gonorrheal arthritis were improved 90 to 95 per cent. Their hospitalization was reduced 75 per cent of that necessary by older methods. The combination of Elliott and "hot box" treatments seemed safer than that of Elliott treatments plus short wave diathermy, which Gurnee also tried.

Fourteen of Owen's 22 patients with gonorrheal arthritis were "cured" by an average of 4.8 periods of fever of 4.6 hours each. Eight patients who only averaged 2.8 periods of five hours each were improved, not cured; failures were due to insufficient heating. "Given patients who can and will take the treatment, better than 80 per cent of gonococcic infections regardless of complications may be absolutely cured in the space of two weeks. . . . This progress in therapy is most appreciated as it applies to arthritis, formerly so painful, time consuming and often permanently disabling." Ability to take treatments depended on the condition of the heart, the resistance of the skin to heating and the patient's temperament. For one reason or another 12 per cent of Owen's patients were unsuitable for fever therapy.

A summary of published results from the treatment of 151 cases of acute gonorrheal arthritis and 32 of chronic arthritis was made by Hensch.

(This also appeared in the third review.—Ed.)

*General Remarks on Fever Therapy.* The institution of fever therapy is not a simple matter to be done in a physician's office by a physician or nurse not specially trained in the technic. It is a highly technical procedure which demands as much care as that required for a surgical operation.



Even in the hands of a well trained personnel complications will occasionally occur; generally they are mild, but sometimes they are serious. Several papers included details on the management of patients under treatment, the contraindications, physiologic effects and complications.<sup>12, 39, 41, 140, 141, 198, 219, 317, 385, 400, 418, 492, 516, 524, 541, 550</sup> The whole subject was extensively discussed in Neymann's review of 332 reports. Other reports noted the beneficial effect of fever therapy in gonorrhea uncomplicated by arthritis.<sup>131, 140, 141, 362, 406, 494, 524</sup>

Contraindications to fever therapy were listed: advanced age, cardiovascular or renal dysfunction, chronic alcoholism, pulmonary tuberculosis, marked debility or emotional instability.<sup>140, 141, 418, 524</sup> The hazards of fever therapy must not be overlooked. Certain patients are brought to the borderline of disaster by degrees of fever not tolerated by them. For details concerning the hazards, complications and accidents incident to fever therapy reference should be made to the reports cited. As Trautman stated, gonorrhea is not a mild disease; it can cause great disability, suffering and economic loss. Therefore the use of fever therapy is justified in spite of occasional failures or disasters. Trautman had experienced no fatalities in the treatment of 238 patients with 1383 fever sessions. Simpson noted no serious complications from 3204 fever sessions given to 431 patients.

(Warren, Scott and Carpenter noted one death in the treatment of 283 cases of gonorrhea in six years. At The Mayo Clinic one death occurred in connection with about 4500 fever sessions given to about 600 patients.—Ed.)

Complications of fever therapy include first degree burns and cutaneous vesicles, diffuse erythema, occasional constipation, diarrhea, anorexia, nausea, headache, herpes labialis, dehydration and exhaustion, tetany, circulatory failure and heat stroke from loss of chlorides and cerebral hyperthermia. One of Stecher and Solomon's patients developed a severe, and two a mild, epileptiform seizure. When Gurnee used the "hot box" alone one of his 27 patients died of heat stroke and two developed severe heat stroke, but no serious effects were noted among his 30 patients treated by combined relatively low general and high pelvic temperatures.

(Details of the instance in which the patient died were not given.—Ed.)

One of Stein's patients with gonorrheal arthritis responded well to two fever sessions, but about 12 days later signs of pyramidal tract involvement were noted which disappeared in two weeks. Three hundred thirty-one episodes of delirium were suffered by 108 of the 200 patients of Barnacle, Ewalt and Ebaugh who had a total of 1324 fever sessions: 204 of the episodes were mild, 118 moderate and nine severe. Delirium averaged 75 minutes (max. 48 hours) and generally occurred in the first fever session. Large, but not small, doses of sedative drugs seemed to predispose thereto.

Additional reports of interest were of the following: electrocardiographic

changes in artificial fever<sup>554</sup>; velocity of blood flow in artificial fever<sup>318, 319</sup>; effects of fever therapy on blood count, blood and urine chemistry<sup>148, 490</sup>; temperatures of superficial and deeper tissues during hyperpyrexia<sup>463</sup>; the relative efficiency of various methods for producing fever<sup>244, 327</sup>; a "satisfactory cheap device" for fever production.<sup>13</sup> The Therma-mode blanket was deemed not acceptable for use in fever therapy. (Council on Physical Therapy of the American Medical Association.)

*Criteria of Cure of Gonorrhea.* These included the following: disappearance of clinical signs of disease and of discharges; presence of clear urine without shreds; absence of gonococci in the shreds when these latter are present; two or three negative smears and cultures; presence of a prostate of normal consistency; prostatic secretion free from leukocytes; absence of urethral flare-up after sexual excitement or after alcohol; in women the presence of no visible cervical irritation, no tubal thickening or tenderness, no flare-up after menses (Brodie, Owens, Pelouze).

*Prognosis; End-Results.* Spontaneous remissions of gonorrheal arthritis may occur with little residual damage "in a fair percentage of cases" (Warren). Certain patients even with gonococcemia may recover under symptomatic treatment alone (Su and Hu; Bakst, Foley and Lamb). However, the chances of residual articular damage are too great to neglect thorough treatment. Kuhns regarded the course of chronic gonorrheal arthritis (untreated by fever therapy) little different from that of other types of chronic arthritis.

(Many believe the term "chronic gonorrheal arthritis" should be restricted to indicate the past history and not to imply a forecast of progressive disease. The term should be used only to indicate that articular symptoms have already existed six weeks or more but not to signify that there is present a chronic progressive arthritis with prolonged symptoms of active inflammation. Gonorrhea rarely (if ever) produces chronic articular disease which progresses independently unless repeated infection or chronic trauma occurs.—Ed.)

#### TUBERCULOUS ARTHRITIS

*Clinical Data.* Current reports include several useful reviews. According to Henderson, the disease is less frequent because of better control of the milk supply and the education of the public on prevention and treatment. Nevertheless, Dickson stated that tuberculous arthritis is responsible for about 20 per cent of all the cripples in the United States. (The basis of this estimate was not given. It seems much too high.—Ed.)

Dickson distinguished between tuberculous monoarthritis (the usual variety), multi-articular tuberculosis (tuberculosis may affect three or more joints in about 5 per cent of cases) and tuberculous polyarthritis or "tuberculous rheumatism" (which will be discussed separately). Tuberculous arthritis can be divided into two stages: 1. The early synovial or pseudosynovial, "preroentgenographic" stage, when the disease is roentgenographically invisible and no osseous foci are obvious; 2. A later stage when more or less definite roentgenographic changes are present.

Early symptoms include: Generally an insidious onset; slight swelling or pain or both; sometimes merely stiffness, local warmth, a limp if the joint bears weight. Constitutional symptoms may be absent or slight: loss of weight, a little fever. As the disease progresses the cartilage becomes eroded, the bone is exposed, pain and stiffness increase and affected children give night cries or there is jerking, especially in hips and knees, from contact of affected bone ends when muscles relax. With progressive bone destruction abscesses may form with or without fever, depending on the occurrence of secondary pyogenic infection. If synovia alone is affected, as occurred in 9 per cent of Henderson's cases, symptoms are chiefly stiffness and swelling. If bone is primarily affected, as is usual, symptoms depend on the situation and size of abscesses. They may exist for years, causing little discomfort. If they break through into the joint abruptly, acute "panarthritis"—involvement of all structures of the affected joint—results. Usually abscesses break through gradually and barriers of protecting adhesions are built up at the site.

In Dickson's 158 cases of tuberculous arthritis, joints involved were as follows: spine in 62, hip in 41, knee in 25, ankle in 11, wrist in 10, sacroiliac in 6, shoulder in 2 and elbow in 1 case.

Multiple arthritis occurred in six of Dickson's 158 cases: the spine was involved in two places once, the spine and knee in two cases, the spine and both hips once, and the knee and wrist, and hip and wrist once each. The tuberculous, or unusual, nature of the polyarthritis was suggested by its asymmetry and the successive, not coincident, involvement of the several joints.

Rare features of tuberculous arthritis are perforation of abscesses of the hip joint, sequestration of parts of the femoral head into the bladder and lengthening of a leg due to stimulation of growth centers by increased vascularity (Henderson). Armstrong noted tuberculosis in a joint which was the site of exostoses typical of metaphysical aklasis, and the presence of extensive tuberculous synovitis in a joint without appreciable stiffness, pain or deformity and without roentgenographic bone changes or pathologic (biopsy) involvement of articular cartilage or bone.

*Pathology.* The usual synovial reaction was described (Ghormley and Deacon).

From a study of four postmortem specimens Compere and Garrison concluded that tuberculous spondylitis begins in cancellous vertebral bone and encroaches on vertebral cartilage and intervertebral disks. Cartilage and *annuli fibrosi*, being resistant to tuberculous invasion, persist longer than bone. As the disease progresses bone is destroyed by the extension of tuberculous tissue which may or may not contain typical tubercles. The anterior common ligament is elevated from the vertebral bodies; the disease extends along the spine beneath this longitudinal ligament, involving vertebrae above and below but not the disks until late. Abscesses may push back into the vertebral canal but do not tend to penetrate dura. The tuberculous processes were compared to those in osteomyelitis.

Vertebral osteomyelitis also seems to begin in cancellous bone via hematogenous implants; as Compere and Garrison noted, it could hardly begin in disks since they

contain no blood or lymph vessels. In contrast to their fate in tuberculous spondylitis, disks in osteomyelitis are quickly destroyed and formation of new bone and vertebral fusion may occur. When tuberculous spondylitis is complicated by pyogenic infection the pathologic reaction is mixed; new bone formation from the pyogenic infection is associated with tuberculous bone destruction.

A case of extensive tuberculous spondylitis which healed under conservative treatment supplied Finder with interesting pathologic material when the patient finally died. The destructive bone changes and osteoporosis, so common in the active stages of tuberculosis, were absent. Bone lesions had healed and osteosclerosis had developed; complete union by bony fusion had occurred between two vertebrae. Finder concluded that healing may occur spontaneously, and vertebral bone sclerosis, as seen in roentgenograms, may indicate an old healed tuberculous lesion, not necessarily osteomyelitis.

*Roentgenographic Features.* They have been presented in previous reviews. They are often only suggestive, not pathognomonic, of tuberculosis. In the early stage none may be present. Later one or more of the following features will be found (Dickson, Henderson): uniform thinning of bone cortex, destruction or thinning of articular cartilages, decalcification of bone ends, lack of new bone formation, presence of foci of bone destruction usually in epiphyses, failure of the process to extend along the shaft but a tendency to involve the neighboring joint. Bone abscesses are indicated by rarefied portions; it is not uncommon to see little notched rarefied areas on tibial or femoral margins at synovial insertions. In a knee the intercondylar notch is often enlarged. In an elbow the olecranon process may be wedged deeply between humeral condyles. In advanced stages the picture is one of destructive arthritis, which is usually more extensive than roentgenograms suggest. The incidence of the various roentgenographic features in 32 cases was noted by Taylor, Ferguson, Kasabach and Dawson. Roentgenograms in tuberculous and gonorrheal arthritis possess several features in common but the length of time required to produce changes in tuberculous arthritis is likely to be ten to twenty times as long as that required to produce corresponding changes in gonococcal arthritis.

*Differential Diagnosis.* Early differential diagnosis is very important since only then, if ever, is cure with function possible. Diagnosis may be difficult because tuberculous arthritis may be multi-articular and atrophic arthritis occasionally may long be monoarticular. Collins and Cameron noted a case illustrating the diagnostic difficulty arising because of the following circumstances: (1) The insidious monoarticular onset of some cases of multiple, nonspecific arthritis, (2) the coexistence in the patient of some visceral tuberculous lesion which may or may not influence the course of nontuberculous polyarthritis, (3) the possible occurrence of a single tuberculous joint superimposed on nontuberculous multiple arthritis, (4) the occasional incidence of true tuberculous arthritis in two or more joints, (5) the comparative infrequency of nonspecific arthritis of a hip in patients of less than

middle age and the tendency to suppose such a condition to be tuberculous, (6) modification of the course of nonspecific arthritis due to early immobilization, (7) the possibility that there exists an atypical tuberculous form of polyarthritis—tuberculous rheumatism.

Consideration of the following factors was currently stressed (Henderson, Dickson, Ghormley and Deacon) as useful in differentiation. Age: Tuberculous arthritis generally occurs before the age of 14 years. However Dickson and Henderson not infrequently noted its appearance in patients 50 to 65 years old. Family history: Familial tuberculosis was present in only 8 per cent of Henderson's cases. Coincident pathology: Tuberculosis occurred in sites other than joints in 44 per cent of Henderson's cases, most often in lungs. Precipitating factors: Recent trauma, 6 to 12 weeks before onset of symptoms, followed by a prodromal quiescent period, was not uncommonly noted. About 50 per cent of patients with tuberculous arthritis think they traumatized the affected joint before onset of symptoms but Henderson believes that trauma really acts as a precipitating factor in only 13 per cent of cases. Appearance of joint: The presence of a chronic or subacute monarthritis should make one suspect tuberculosis. The characteristic appearance is that of a boggy joint without evidence of acute inflammation, a doughy enlargement due to swollen synovia, not to hydrops. Generally little or no fluid can be felt or aspirated from a tuberculous joint in contrast to the hydrops common in nonspecific arthritis. Much fluid is evidence against, rather than for, tuberculosis. Muscle atrophy is present, often early and extreme—out of proportion to the duration of illness. Symptoms: The rather late appearance of articular pain and tenderness suggests tuberculosis; in other arthritides pain is usually early and notable. Course: A feature of tuberculous arthritis is its indolent chronicity with periods of remission and exacerbation; the general trend is one of progression and persistence of symptoms, a residuum of symptoms remaining even in the so-called remissions.

*Biopsy and Guinea-Pig Tests.* The diagnosis of tuberculous arthritis is not easy. Biopsy is sometimes necessary. Pathologists are usually able to make a definite diagnosis but in doubtful cases guinea-pig tests are necessary. Studying 175 cases of suspected tuberculous arthritis, W. E. Swift noted the relative accuracy of diagnosis made on the following: clinical data, roentgenograms, frozen-sections of tissue, paraffin-sections of tissue, inoculation of guinea pigs. Each method was subject to some error.

*Tuberculin Reaction.* A positive tuberculin reaction affords only presumptive evidence of tuberculous joint disease unless all other possible active tuberculous foci can be excluded. A negative reaction in the absence of certain modifying factors (overwhelming tuberculous infection, advanced sepsis, anemia or other grave disease) can eliminate the diagnosis of tuberculosis with some certainty. Collins and Cameron recommended Parke-Davis' Tuberculin P.P.D. (Purified Protein-Derivative) for such tests.

*Treatment.* In 50 per cent of the 400 cases in which arthrodesis was



done at The Mayo Clinic for tuberculous spondylitis there was arrest of the disease, according to Henderson. Eradication of tuberculous bone is not possible and the operation of fusion of laminae and articulating processes posteriorly, if combined with general treatment, seems merely to hasten the process of arrest of the disease. For tuberculosis of the hip arthrodesis by combined intra-articular and extra-articular fusion was favored: results were successful in 90 per cent of 46 cases. The conservative nonsurgical treatment for tuberculous knees is preferable in children but not in adults; in the latter, surgical treatment is preferable because of the economic problem. Whether arthrodesis is to be done depends on the condition of the knee and the patient's general condition, social status, temperament, and so forth. A low grade tuberculous arthritis of a knee may exist for years with little trouble to one able to govern his activities; in such cases arthrodesis should not be insisted on. Bony fusion was successful in 89 per cent of Henderson's 248 patients with tuberculous knees; the surgical mortality was zero. For the treatment of quiescent tumor albus and tuberculous pseudoarthrosis in children Delahaye developed a completely extra-articular method of arthrodesis. In a tuberculous hip the production of solid, bony ankylosis is the best result that can be obtained; even so abscesses may develop and sinuses may continue to drain indefinitely, according to Adams.

#### "TUBERCULOUS RHEUMATISM"

*Definition; Types.* Poncet (1897) described two varieties of tuberculous rheumatism or polyarthritis: an acute or subacute form and a chronic form. Basis for the diagnosis included a family history of tuberculosis and the presence in the patient of true tuberculous arthritis occurring before, with, or after the onset of the "tuberculous polyarticular rheumatism." Since Poncet, others have varied the clinical picture and extended the basis of diagnosis. According to Copeman, one variety resembles acute rheumatic fever in that joints are successively affected without permanent lesion or disability but it differs from rheumatic fever in the absence of carditis and resistance to salicylates. The second variety is that of a transitory or more chronic polyarthritis eventually becoming localized in one of the joints first affected.

*Clinical Features.* Admittedly the clinical features of the entity have never been set forth with unmistakable clarity. Kubirschky's criteria for a diagnosis of tuberculous rheumatism were repeated.<sup>145, 247</sup> Reputed clinical features are as follows (Copeman, Dickson): (1) tuberculosis often in the affected person's family, (2) visceral tuberculosis often in the affected person, (3) involvement of fewer joints than in most types of polyarthritis and a predominant involvement of one joint, (4) presence of more fever than in other forms of polyarthritis, (5) a condition refractory to salicylates, (6) absence or rarity of carditis, (7) isolation of Koch's bacillus from synovial fluid in certain cases, (8) blood cultures positive for tubercle

bacilli (Reitter-Löwenstein technic, 1934), but only during certain phases of the disease.

*Representative Cases.* Copeman found 12 cases in the literature which seemed to fulfill these criteria. Most of them were reported from France; none from England or America in 22 years. Six of the 12 cases seemed to represent an intermediate type, "not so far recorded in the English literature," in which pathologic reaction in patients' joints were atypical but injections of joint fluid produced tuberculosis in guinea-pigs.

Of the 12 patients, 10 were females; two were males. Age onset of arthritis averaged 28 years (range 17 to 66 years); three gave a history of previous attacks, with increased joint damage after each, the joints in the intervals being quiescent; eight noted febrile onset; four of six patients were unrelieved by salicylates; three gave a family history suggestive of tuberculosis; four previously had disease suggestive of tuberculosis; two ultimately developed frank tuberculous arthritis in one of the affected joints; all of five patients tested had positive tuberculin tests; joint fluid from eight cases and blood from one case were injected into guinea-pigs; results were "positive" for tuberculosis in six, doubtful in one, negative in two; in four cases synovial tissue at biopsy revealed "chronic inflammation"; in two specimens acid-fast bacilli were seen on staining; in five cases ankylosis occurred in one or more joints.

Applying these criteria and tests to 42 of his own cases of "typical rheumatoid arthritis" Copeman detected evidence of an associated tuberculous factor in 12 cases.

(Two of these cases were abstracted in the third review.—Ed.)

He concluded that a proportion (possibly 30 to 40 per cent) of all patients with true rheumatoid arthritis can be shown to suffer or have suffered from a low-grade tuberculous infection, which in certain cases at least may be related to the course of the polyarthritis, and that "tuberculous rheumatism" cannot be distinguished by clinical means from rheumatoid arthritis of other causation. Features most suggestive of the condition were the increased incidence of tuberculous antecedents (present in six of his own 12 cases); subsequent development of classical tuberculous arthritis (in two of the 12 cases); the discovery, after injection of tuberculin, of silent foci of tuberculosis (in two cases); pyrexial onset of the arthritis with marked fatigue (three of 12 cases); increased sensitivity to tuberculin in all of 12 cases; a tendency for the condition to progress by recurrent attacks with intervening quiescent periods; the isolation of tubercle bacilli from the blood (sent by Copeman to Löwenstein) of 11 of the 12 cases. Specimens of blood from 30 patients with rheumatoid arthritis in whom Copeman found no evidence of associated tuberculosis were also sent to Löwenstein; in only one case was the culture "positive for Koch's bacillus," the case of a child whose father was being hospitalized for tuberculous adenitis.

*Pathogenesis; Pathology.* Copeman's interpretation follows: Most persons have been infected with tuberculosis in early life but have overcome the infection. In certain cases focal areas may become quiescent or slightly

reactivated but "silent." Certain cases of "rheumatoid arthritis of unknown cause" are cases of tuberculous rheumatism, the infection originating in a chronic or periodic leakage of toxic material, or of actual bacilli, possibly of attenuated virulence, from such a tuberculous focus. This primary focus is of such low virulence as to cause no general symptoms but it produces in "susceptible" joints an inflammation different from classical tuberculosis. The histologic appearance of synovia generally reveals "non-specific inflammation" with subendothelial collections of round cells as found in rheumatoid arthritis. Perhaps the latter cells represent a halfway stage, due to altered bacterial virulence, between nonspecific and true tuberculous changes. Perhaps the affected joints are sensitized by tubercle bacilli, their toxins or virus; this sensitization may be nonspecific to the extent that subsequently it can be activated by streptococci or other bacteria, not necessarily tubercle bacilli, thus presenting a "symbiotic cause" of chronic polyarthritis.

*Conclusion.* The consensus of current opinion is that this entity is not established. Those who refuse to accept it base their position on the failure to find characteristic histologic changes in repeated examinations of tissue from supposed cases and the negative results of guinea-pig tests. It was agreed that there seems to be no good reason why tuberculosis cannot produce a polyarthritis just as streptococci or gonococci do. One cannot categorically deny the possible influence of associated visceral tuberculosis on the production and course of polyarthritis. However, no definite clinical syndrome of tuberculous rheumatism has been established, no consistent experimental or laboratory evidence has been produced in support of the clinical evidence offered, and in very few of the reported cases has proof of tuberculous origin been forthcoming. According to Ghormley and Deacon, "To date no proof of the tuberculous etiology of chronic proliferative arthritis exists. It may be proved at a later date but this seems unlikely to us."

#### SYPHILITIC SYNOVITIS AND ARTHRITIS: CHARCOT JOINTS

*Charcot Joints.* The incidence of Charcot's disease in neurosyphilitic patients is not great. It developed in 6 per cent of 744 tabetic patients (Moore, 1933). Epstein's patients with Charcot joints rarely presented themselves because of symptoms referable to their nervous system but because of joint disease. The condition was not accompanied by any marked symptoms of tabetic disease.

*Pathogenesis.* Epstein accepted the theory of Wile and Butler (1930): the joint changes are always associated with destruction of the afferent (proprioceptive) nerves, rendering the joint tissues insensible to trauma. Under these conditions each minor injury or even physiologic trauma produces further articular pathologic lesions which accumulate to form the end picture of a Charcot joint. Many restrict the use of the term "Charcot

joint " to the arthropathies of neurosyphilis. But articular disintegration similar to tabetic arthropathies may occur with syringomyelia, myelitis, poliomyelitis and gunshot wounds of the cord.

*Roentgenograms.* Except in early cases the changes are fairly typical: swelling and increased density of soft tissues, excess fluid in joints and tissues, diffuse sclerosis of bone with atrophy, erosion of joint surfaces, production of new bone, pathologic fractures, loose bodies in the joint, calcification in periarticular tissues, subluxations or dislocations (Epstein).

*Cytology of Synovial Fluid.* Collins studied the fluid from a grossly disorganized Charcot joint of a patient who had advanced tabes. The total cell count was 250 per cu. mm., with 25 per cent polymorphonuclears and 43 per cent lymphocytes.

*Treatment.* Neurologists and syphilologists have been able to do little in these cases. Orthopedic management is more important than antisyphilitic treatment, according to Epstein, who presented eight cases in which antisyphilitic treatment alone was insufficient to check the progress of arthropathy. Conservative treatment to reduce pain and swelling and to protect the joint from trauma includes much rest; avoidance of weight-bearing; immobilization in a splint or cast if necessary; local application of heat, especially diathermy; non-weight-bearing exercises; if fluid is present, repeated aspiration to prevent undue capsular and ligamentous stretching; later suitable orthopedic supports for affected joints. Operative treatment includes correction of fractures, removal of draining sinus tracts, amputation of totally disintegrated regions such as an ankle or foot that has become "a veritable bag of bones," correction of valgus or varus position of an ankle by osteotomy, and other procedures.

*Fever Therapy and Chemotherapy as Prophylaxis.* Since the only effective treatment of Charcot's disease is prevention it is appropriate to note that electropyrexia represents a distinct advance in the treatment of early syphilis and of neurosyphilis particularly when combined with chemotherapy (Simpson, Neymann, Lawless and Osborne). "Tabes is very favorably influenced by electropyrexia." Neymann, Bennett and Simpson noted relief from intractable root pains, gastric crises, ataxia, cord bladder, head pains, and paresthesia. Fever therapy should not be expected to affect Charcot joints.

#### UNDULANT (MALTA) FEVER; BRUCELLOSIS; BANG'S DISEASE

*Incidence.* A discussion of undulant fever is appropriate because the disease commonly affects muscles and joints. Further data were presented on the increasing prevalence and recognition of the disease in the United States and in the separate states (Hardy, Jordan, and Borts); in Kentucky (Beatty); in Pennsylvania (Ervin, Hunt and Niles); in Wisconsin (Sprague); in Texas (Winans), and in the Tanganyika Territory (Wilson). Reported cases in the United States numbered 1,887 in 1934; 1,897

in 1935. The highest incidence is in Iowa, Vermont, Missouri and Kansas. There were 705 new cases in Iowa. According to Winans, brucellosis in office practice in Texas is more common than unsuspected syphilis. Among 295 office patients studied in sequence, 10 had positive agglutination tests for undulant fever; seven gave a positive Wassermann test. Discarding patients with no other signs of the disease the corrected total of cases of clinical undulant fever was 1.7 per cent of the 295 patients.

*Economic Importance.* Undulant fever is the greatest medical problem in the cattle industry. Apparently 20 per cent of all cows in Texas (Green), 10 per cent of all milk goats, and 13 to 16 per cent of cows in the entire country have or have had the disease (Vreeland).

*Symptoms.* "A disease of many forms, undulant fever in the human has no parallel; it may be latent or fulminating, acute, subacute, or chronic, local or general, febrile or afebrile, inflammatory or noninflammatory" (Green). Its symptomatology is protean and widespread and may be classical to the experienced physician but vague and mixed to the unsuspecting practitioner. Textbook descriptions are inadequate and ordinarily would not lead to a diagnosis. Laboratory data and the incidence of various symptoms were studied in 705 cases by Hardy, Jordan and Borts; in 300 cases by Dalrymple-Champneys; in 35 cases by Beatty; in 12 cases by Ervin, Hunt and Niles. Dishongh regards the disease as without cardinal symptoms; as one "which may resemble any disease known to science." Symptoms are those of septicemia. Commonest were weakness; fatigue; malaise; fever; drenching sweats; headache; "rheumatic pains" in various muscles and joints, in back, neck, chest or extremities; anorexia; constipation; chilliness or chills; epigastric, abdominal or pelvic pain; palpitation; depression; weight loss. There were a host of less common symptoms. Occasional complications were sinusitis, pyelitis, pleurisy, mucous colitis, seborrheic dermatitis, leg ulcers.<sup>81, 127</sup>

The fever is usually intermittent, remittent or undulating; but this type is not always present (Gottlieb). Secondary anemia and leukopenia with relative lymphocytosis are usually present but leukocytosis occasionally occurs.<sup>209</sup>

Five clinical types were spoken of: 1. The intermittent type, which is the commonest, is of subacute onset and there is an intermittent afternoon fever; the average duration is 1 to 4 months. 2. The ambulatory type comprises 25 per cent of cases in the United States; the illness is short and mild and is featured by weakness and fever which may be high but which is quite or almost unrecognized by the patient, who may continue at work. 3. The undulant type (15 per cent incidence) is marked by successive relapses, decreasing in intensity and duration. 4. The malignant type (2 per cent of cases) is of sudden onset; it is an overwhelming disease of rapid, fatal termination. 5. The subclinical type is unrecognized by the patient; it is asymptomatic, affects exposed persons and is discovered by the presence of agglutinins. The disease presents two phases: 1. The acute phase may have



an insidious or sudden onset. Prodromes are malaise and general aches; later symptoms are chill, fever, headache, backache, neckache, sweating, weight loss, acute arthralgia, abdominal pain, nausea, vomiting. 2. The chronic phase may follow the acute, or may appear independently, and is characterized by malaise, low grade fever, growing weakness, weight loss, general aches and pains. The disease is most commonly misdiagnosed as typhoid fever, influenza, paratyphoid fever.

Duration of the disease is very variable: according to Beatty, who studied chronic cases, it may last four weeks to 17 years (av. 37 months); according to Carpenter and Boak it generally lasts ten days to six months, occasionally six years (av. three months). To determine the natural course of the disease without "specific treatment" Carpenter and Boak treated 26 patients symptomatically only; the duration was two to 72 (av. 12.5) weeks.

Symptoms referable to muscles and joints: In different reports the incidence of articular symptoms was variable but generally notable: arthropathies were present in 31 per cent of Simpson's 175 cases (1930), in 32 per cent of Hardy's 375 cases which also included one case of hydrarthrosis and one of osteomyelitis. Undulant fever in Iowa has been characterized by arthritis, acute or chronic, septic or nonseptic, by spondylitis simulating Pott's disease, and by osteomyelitis (Hardy, Jordan, Borts). Wilson regarded as "very characteristic" burning pains in certain joints, especially wrists, ankles, elbows. Dalrymple-Champneys noted "arthritis and arthralgia" (no further description) in 20 of 300 cases. Four of the eight patients noted by Neumann had "rheumatic pains"; one other patient had arthritis of a hip joint. Other cases of undulant fever with arthritis were noted.<sup>79, 147, 511, 555</sup> Two of Vreeland's patients had four joints severely affected; one patient, six joints. A patient of Winans had fever, pain, swelling and stiffness in ankles, wrist and spine, a negative agglutination test and blood culture but a strongly positive skin test and rapid response to appropriate treatment. Cases with arthralgia and myalgia were noted by many.<sup>168, 555</sup> Among Beatty's 28 patients, 24 had backache, 23 had neckache. According to Sprague "rheumatic manifestations," pain and swelling in joints, have been reported in about 50 per cent of cases; Vreeland often noted swollen, tender but not red joints, especially shoulders, ankles, knees, hips and sacro-iliacs.

Kulowski noted five cases of undulant fever affecting the osseous system: two cases of spondylitis, one of acute arthritis of a wrist, two of osteomyelitis (of the humerus in one instance; of skull and ribs in the other).

*Case 1.* Brucellosis osteomyelitis of left humerus. The patient noted insidious onset of pain and stiffness of the left arm and shoulder, which continued for four years without constitutional reactions. An abscess finally formed and was drained. Pain recurred and a deltoid sinus was incised. Brucella organisms were recovered; agglutination test was strongly positive.

*Case 2.* Brucellosis spondylitis. A month after "the end" of a 6½ months'

undulant fever, low back pain developed without constitutional reaction. The condition became acute and febrile. Agglutinins for *Brucella* were present—1:640 and 1:160. Spinal fusion was done.

*Case 3.* Brucellosis spondylitis. Low backache developed, remained insidious for seven months, then became acute. Roentgenograms showed destruction of lower lumbar interarticular facets with abscess formation. A huge prevertebral abscess was drained; *Brucella* was recovered.

*Case 4.* Brucellosis of wrist joint. Undulant fever developed; agglutination, 1:640. Three months later acute painful swelling affected a wrist from which pus was recovered.

*Case 5.* Brucellosis osteomyelitis of skull and ribs. Undulant fever developed in May. An abscess appeared over the ribs anteriorly in June, another abscess over a hip in September, other rib abscesses in October 1930. In September 1933, a skull lesion was drained; pus was sterile.

Intermittent hydrarthrosis associated with undulant fever was noted once each by Baker (1928, 1929), by Weil (1930), by Hardy and associates (1931) and by Simmons (1935). Sharpe has reported another such case:

A young man, in 1929, had painful swellings of knees, right ankle and right wrist. These persisted for 6 weeks, recurred at irregular intervals in the knees for a year. Fever was not noted. The knee swellings returned in 1933, were definitely intermittent, sufficiently painful to require repeated aspirations, and were associated with afternoon fever to 102° F. Anorexia and loss of 20 pounds had occurred. The swellings occurred in 7 to 10 day cycles; between times they disappeared completely from the left knee, incompletely from the right and were painful only at their highest level. The patient had lived on a farm, adjacent to those affected with contagious abortion, and had drunk cow's raw milk. Roentgenograms indicated "rheumatoid arthritis." Agglutination tests with *Brucella* were 1:400. Cultures of blood, urine and synovial fluid for *Brucella* were repeatedly negative. Fever and articular swellings were unrelieved by a course of Lederle's undulant fever vaccine, only partially and temporarily relieved by artificial fever therapy. Fever, hydrops and strong agglutination reactions have persisted.

(Was this really a case of undulant fever?—Ed.)

With Scott, O'Donoghue, who recently noted a septic hip due to *Brucella* (1933), reported a case of degenerative myositis from *B. melitensis*:

The patient had fever, agglutination 1:320, a positive skin reaction and was treated by goat serum and brucellin. During treatment shoulders and deltoids became painful. Within a month atrophy of supraspinatus and infraspinatus muscles and of the deltoids occurred but disappeared 10 months later. Biopsy disclosed degenerative myositis, interstitial round-cell infiltration, sterile cultures.

*Diagnostic Criteria: Laboratory Data.* A diagnosis of undulant fever depends on the presence of a characteristic or a suggestive history supported by some of the following:

1. *Agglutination Tests.* The agglutination test is the most valuable diagnostic test after the first two weeks of the disease (Ervin, Hunt and Niles); it is most dependable in the active stage of the disease or when patients have recovered recently (Keller, Pharris and Gaub). Agglutinins against *Brucella* organisms are generally significantly present after 5 to 14

days of illness (Dalrymple-Champneys, Sprague) but it may take several weeks for tests to be definitely or strongly positive (Gottlieb). The agglutinin content of blood may change rapidly; repeated tests are often necessary before a positive test is obtained (Beatty, Dalrymple-Champneys). Titers are generally present in dilutions 1:80 or higher (Gottlieb, Sprague) but even in definite cases of brucellosis, titers may be low: 1:50, 1:10, or even negative (Beatty, Sprague). Five per cent of patients never develop agglutinins (Beatty). Of 100 cases seen by Huddleson, Johnson and Bates, agglutinin titers were negative or less than 1:50 in 33 per cent. Among Dalrymple-Champney's 255 cases, the average titer was 1:1500; it rose as high as 1:2500 and in only one case was it less than 1:100. Among Beatty's 35 cases the titer was 1:100 or over in 26, 1:50 in six, 1:25 in one and negative (but with positive skin tests) in two cases. A negative agglutination test means either that brucellosis is absent, or that the disease is present but there is no immune response (Kemp). Agglutinins may be present for months or years after clinical recovery and titers were frequently as high as 1:640 after 4½ years (Dalrymple-Champneys). (Meanwhile an unrelated atrophic arthritis could develop. Therefore every polyarthritis with positive agglutinins for *Brucella* must not be attributed to brucellosis.—Ed.) After clinical recovery titers usually fall rapidly; a continued high titer suggests latent activity. Donham and Fitch developed a modified technic to discover agglutination earlier.

2. *Precipitin Tests.* Sera from patients with positive agglutination reactions also gave positive precipitin reactions with one or more polysaccharides but Higginbotham and Heathman consider the precipitin tests less practical than agglutination tests.

3. *Complement-Fixation Tests.* Although Thomsen (1931) found these positive oftener than agglutination tests, others<sup>209, 262</sup> found them more difficult and not as reliable as agglutination or precipitin tests.

4. *Intradermal Test.* The technic and interpretation of this test were again described.<sup>81, 127, 298, 581</sup> *Brucella abortus* antigen is used. Tests become positive after 7 to 11 days of disease (Sprague). A positive test is especially helpful for diagnosis in active cases when agglutination tests are negative (Ervin, Hunt and Niles). A diagnosis should not be made only on the basis of a positive skin test: 20 per cent of residents in certain communities give positive tests (Carpenter and Boak). Tests were positive in 5 per cent of one group of 576 persons, living or working under conditions favorable to *Brucella* infection (Keller, Pharris, and Gaub). Kemp considered them more reliable than tuberculin tests in tuberculosis; a positive test may be incidental to a given diagnostic problem as it indicates previous as well as active infection (Gottlieb).

(The antigen is irritating. Controls should always be tested simultaneously with suspects.—Ed.)

When it is desired to study both agglutination and intradermal tests,

agglutination tests should be done first because injections of the amount of material used for skin tests will of themselves promote agglutination reactions in titers of 1:50 to 1:200, thereby providing a source of error (Winans).

5. *Cultures.* The organism may be isolated by special technic<sup>127, 576</sup> from blood, urine, feces and other sources. Cultures of blood are more successful than those from other material; even so they are often negative, difficult to make, and less often used for diagnosis than other tests.<sup>298, 511</sup> However, much can be learned therefrom regarding types of strains and they should be made oftener.<sup>236</sup> They usually become positive 3 to 15 days after the patient's inoculation.<sup>555</sup> They were positive in 16 of 85 cases (Huddleson and associates). Poston and Smith recovered *Brucella* from spinal fluid by a new technic whereby the germs can be grown after being precipitated by specific agglutinating serum.

6. *Guinea-Pig Inoculations.* These are unsatisfactory as the test requires 4 to 6 weeks' observation and lesions resemble tuberculosis (Kemp).

7. *Opsonophagocytic Activity of Blood.* This test was originated by Huddleson, Johnson and Hamann (1933); its value in determining a patient's immunity was confirmed by Keller and associates, who discussed technic and interpretation. With it, in conjunction with the skin test, one can determine which patients are susceptible, infected, or immune to undulant fever.

A low phagocytic activity and a negative skin test indicate susceptibility to brucellosis. A low or negative phagocytic activity with a positive skin test indicate infection without immunity. Marked phagocytic activity indicates developing or established immunity. Marked phagocytic activity and a positive skin test indicate that fever in a given case is due to some disease other than undulant fever.

8. *"Therapeutic Test."* Most of Beatty's patients with undoubted brucellosis noted accentuation of symptoms, malaise, general aching, as a reaction to intramuscular injections of undulant fever vaccine. Beatty considered this reaction of diagnostic significance.

#### TREATMENT OF UNDULANT FEVER

After reviewing 67 reports Carpenter and Boak regarded the efficacy of specific therapy unproved. The disease is self-limiting, subject to spontaneous remission or cure. They found no definite evidence that "specific therapy" shortened the disease; symptoms lasted an average of 12.5 weeks in those treated "specifically," 11.3 weeks in those treated symptomatically. General measures for the disease were again stated.<sup>127, 581</sup>

*Chemotherapy; Intravenous Antiseptics.* Various chemicals, arsenicals, dyes, acriflavine, and so forth, produced no beneficial effect unless a febrile reaction was induced.<sup>31, 70, 299</sup>

*Specific Vaccine.* Twenty-seven reports noted results in 350 patients treated with stock or autogenous vaccines. Results obtained had little to do

with the type of vaccine used but depended on the production of systemic reactions.<sup>79</sup> Among 21 other patients only four were benefited by stock vaccine, only one of six benefited by autogenous vaccine (Dalrymple-Champneys). It was considered "beneficial" by Dishongh, "helpful but not curative" by Winans, "fairly satisfactory" by Beatty all of whose 23 patients were improved, some markedly, others slightly.

*Toxic Filtrates.* These produced no effect unless "shock" was induced (Carpenter and Boak).

*Brucellin.* This seemed useful to some<sup>275</sup>; in 100 cases the average illness before treatment was 159 days; after treatment, 18 days.

*Antiserum.* Results with convalescent and animal sera noted in 13 reports were generally favorable, not spectacular (Carpenter and Boak). Superior to his older serum is Foshay's new antibrucellosis (horse) serum which is definitely antitoxic according to Bannick and Magath. Poston and Smith treated two patients successfully with intrathecal injections of human immune serum. Two patients were successfully treated with immunotransfusions by Creswell and Wallace who used the opsonophagocytic index in selecting donors.

*Foreign Protein Therapy.* Wilson, and Carpenter and Boak occasionally noted rapid recovery and excellent results from the shock and fever reactions of T. A. B. (triple typhoid) vaccine. Results in 12 cases of Ervin, Hunt and Niles were "uniformly successful" because of febrile reactions which presumably stimulated specific or nonspecific immunity. After three to six doses of the vaccine, symptoms cleared and agglutination tests became negative. Nine of the 13 other patients were also definitely helped thereby (Dalrymple-Champneys).

*Fever Therapy.* Carpenter and Boak treated three patients with artificial fever: two were promptly cured; one patient's symptoms, including arthritis, were stopped but a year later "the specific arthritis" returned. Recalling the good result noted by Simmons (1935) who treated by means of artificial fever a case in which the disease was associated with severe hydrarthrosis, Prickman and Popp treated four patients without arthritis. Prompt results were obtained with three fever sessions, each for five hours at 105 to 107° F. Curiously the natural fever continued until the last fever session, then stopped rather abruptly, not before. *Brucella abortus* in vitro can survive 24 hours at 107° F.<sup>545</sup> Therefore fever therapy alone probably does not kill the bacteria in vivo; corollary cytologic and immunologic reactions are stimulated.

*Fouadin (Antimony Bis-Pyrocatechin Disodium Sulphonate).* This substance injected intragluteally benefited eight of Neumann's patients.

*Criteria of Cure; Mortality.* Angle's (1935) criteria of cure were (1) disappearance of subjective symptoms, (2) increasing weight, (3) gradual disappearance of fever, (4) lowering of agglutinin titer, (5) return of normal blood picture, (6) subsidence of neurologic symptoms. The reported mortality is 1 to 4 per cent; in severe outbreaks, however, it may be as high as



13 per cent.<sup>511, 555</sup> Death in one series resulted in two of 100 cases<sup>275</sup>; in nine of 290 other cases,<sup>127</sup> in one of 26 patients,<sup>79</sup> and one of 35 cases.<sup>31</sup> Gottlieb's patient at death exhibited usual features; splenitis, lymphadenitis; also, rare features: subdiaphragmatic and hepatic abscesses.

*Prophylaxis.* This can be accomplished by using only boiled or pasteurized milk, and by inspection of herds—the use of blood tests for all cows and goats and the segregation, or preferably destruction, of affected animals.<sup>31, 211</sup>

#### TYPHOIDAL SPONDYLITIS: "TYPHOID SPINE"

Cases of typhoid fever, especially "typhoid spine," are now rare in the United States. A few members of the Civilian Conservation Corps recently developed typhoid fever in Texas; one developed "typhoid spine" (Bowen and McGehee).

Positive blood cultures proved the diagnosis of typhoid fever in a boy, aged 15 years. After desperate illness for two months he convalesced one month, then developed dorsal scoliosis, lumbar pain and rigidity. Roentgenograms showed typhoid spondylitis in various stages. Treatment included immobilization of the spine on a Bradford frame; later a brace was worn for six months.

Typhoid spondylitis may occur during the fever or during convalescence. It produces paroxysmal attacks of intense pain, tenderness, and muscle spasm, generally lumbar. Roentgenograms show localized areas of rarefaction near corners of vertebral bodies, thinning of disks, subsequently the development of a heavy bony bridge about the focus and disk. Suppuration has not been noted.

Campbell and Greenfield found post-typhoid suppurative osteitis in a case previously called "rheumatism."

In 1922 the patient, a young man, had typhoid fever. Long afterward he was still a typhoid carrier. Ten years later, without intervening illness, he developed a painful left arm, diagnosed "rheumatism." Pain recurred the next year without fever, rose spots, splenomegaly or other features of typhoid fever. A bone abscess in a humerus was drained; a pure culture of *Bacillus typhosus* was obtained therefrom. The agglutinin titer was 1:250.

#### MENINGOCOCCIC ARTHRITIS

Joints are involved in 4 to 7 per cent of cases of meningococcic meningitis.<sup>246</sup> A case of meningococcal suppurative arthritis of cryptogenic origin was reported by Campbell and Greenfield.

A colored infant, aged 15 months, developed an inflamed knee joint with fever of 103° F. Pus was removed therefrom; the child improved immediately. Cultures of pus revealed *Neisseria intracellularis* which agglutinated with polyvalent meningococcus agglutinating serum up to a titer of 1:100 of the serum. The patient did not have meningitis.

*Fever Therapy for Meningococcic Infections.* Sustained artificial fever at 107° F. is effective against certain strains of meningococci. Thermal deathtime studies by Bennett, Person and Simmons showed that most strains died out on a water bath at 106.8° F., within eight hours. Two cases of proved chronic meningococcic infections (neither with arthritis), were cured by artificial fever. Artificial fever therapy will probably not replace serum therapy; because of the danger of severe cerebral edema and medullary failure fever therapy is probably contraindicated in acute meningitis. It may have a place as adjuvant therapy in subacute or chronic meningococcic infections unrelieved by serum or in meningococcemia.

#### PYO-ARTHRITIS: PURULENT (SEPTIC) ARTHRITIS

Acute septic arthritis arises in three ways. Bacteria reach the joint: (1) By direct introduction into joints from penetrating wounds; knees are thus affected most often but this is the least common type of septic arthritis in civil life; (2) by direct extension of para-articular infection, most commonly osteomyelitis, into a joint; (3) by the blood stream from distant foci of infection. This type, "metastatic arthritis," is the most frequent and may follow measles, scarlet fever, gonorrhea, pneumonia, meningitis, subacute bacterial endocarditis, in association with any septicemia; for example, from abscesses in tonsils, teeth, or prostate, from boils or infected skin, from scratches or wounds. Of seven cases of septic arthritis of hips in children seen by Freiberg and Perlman, six originated from otitis media or mastoiditis, one from trauma, one from unknown source. Of 16 cases affecting knees seen by Eggers, seven originated from puncture wounds or other trauma, one from pharyngitis, three from pneumonia, one from osteomyelitis, four from other causes. Regan's four cases in hips arose from cystitis, sinusitis, oral infection, tonsillitis.

Invading bacteria are generally *Staphylococcus aureus* or hemolytic streptococci; less commonly other streptococci, gonococci, pneumococci, meningococci, typhoid bacilli, influenza bacilli (Harris). In current series organisms recovered were staphylococci, hemolytic and nonhemolytic streptococci and pneumococci (Eggers, Freiberg and Perlman, Regan).

Clinical findings as currently reviewed are usually definite: abrupt onset of pain, redness and swelling of a joint, often after trauma; capsular distention; muscle spasm in flexed position; marked constitutional reactions; fever; leukocytosis; sometimes positive blood cultures. Aspiration of the joint reveals pus and confirms the diagnosis. Badgley and his colleagues reported 113 cases of septic hips.

*Pathology.* Depending on the severity of infection, pathologic reactions vary from mild synovitis to a devastating articular infection that may end in death. They were briefly summarized in recent articles.<sup>9, 194, 195, 238</sup> Most important are changes in cartilage which, once destroyed, is not replaced. Variable degrees of destruction occur, not by the direct action of bacteria

but by the action of proteolytic enzymes in the leukocytes of pus, to a lesser extent by pressure and by synovial pannus. The microscopic appearance is the same in various pyo-arthroses irrespective of the invading bacteria.

*Roentgenograms.* In the early stage roentgenograms show little or nothing in the hematogenous type of septic joints. In other types they may reveal penetrating wounds or osteomyelitic foci.<sup>9, 238</sup> Later, variable degrees of destructive arthritis are seen but then roentgenograms are of no diagnostic, only of prognostic, help.

*Differential Diagnosis.* Differentiation must be made from rheumatic fever, gonorrheal arthritis (which may also produce septic joints), juxta-articular osteomyelitis without secondary arthritis, less often hemophilic arthritis.<sup>9, 238</sup> In osteomyelitis of juxta-articular bone, maximal tenderness, swelling and pain are over the epiphyseal line rather than the joint. If the joint is still not secondarily affected it moves without pain through a partial range of movement. The most valuable clinical symptom in differentiating acute septic arthritis from periarticular lesions is that the patients with septic arthritis often have severe pain on the slightest degree of passive motion, induced even when adjacent muscles are completely relaxed (Armstrong).

Diagnosis is easy when classical symptoms are present: initiating trauma or infection, fever, leukocytosis, one swollen painful joint, generally in a child. All writers emphatically urged that in case of doubt diagnostic aspirations, repeated if necessary, are urgently indicated. "Their value cannot be overemphasized." By aiding early diagnosis they provide the only sure means of protecting the joint, which will be seriously damaged or perhaps completely destroyed if diagnosis is delayed.<sup>9, 160, 238</sup> According to Armstrong, "monarticular lesions should always be considered septic until proved otherwise."

(We agree that *acute* monarthritis with marked *constitutional reactions* should always be regarded as septic arthritis until proved otherwise. Commonest forms of acute monarthritis (much commoner than septic arthritis) are traumatic arthritis, nonseptic gonorrheal arthritis or gouty arthritis. In acute gouty arthritis the local pain and inflammation may be intense but constitutional reaction is usually mild.—Ed.)

When a wound occurs in the vicinity of a joint it is sometimes difficult to determine whether or not it has entered the joint. Harris' procedure is to insert a needle into the joint distant from the wound and inject a small amount of ether; if the wound penetrated the joint ether will boil out of the wound.

*Complications of Septic Arthritis.* The following complications were noted by Badgley and his colleagues among 113 cases of septic hips: disappearance of the femoral head in 43 cases, sequestration of femoral head in 21 cases, epiphysiolysis in nine cases, dislocation of the femoral head in 34 cases, nearthrosis at the epiphyseal line with fusion of head to acetabulum or ilium in eight cases, coxa magnum in 5 cases. Freiberg and Perlman observed seven cases in which inguinal lymphadenitis and iliac abscesses

were secondary to septic hips. "No similar cases have been reported previously." The question was raised: Are secondary iliac abscesses unrecognized but common complications of septic hips? Hepler noted five cases of septic hips from pelvic osteomyelitis in which the bladder became markedly displaced by intrusion into the pelvis of an enormous involucrum to which the bladder became attached and was displaced laterally. In such cases perforation of the bladder by sequestra and production of osteovesical fistulas threaten or impend. When perforation occurs, as it did in two cases, it is chronic or subacute, with the entire side of the bladder firmly adherent to the involucrum so that there is no urinary extravasation or leakage, and no signs or symptoms referable to the urinary tract. Therefore cystograms should be made routinely, as the condition occurred in every child with chronic suppurative arthritis of the hip and pelvic osteomyelitis which Hepler saw in the last six years.

(One of us, J. A. K., believes these cases are very unusual and that such routine cystograms are not advisable.—Ed.)

*Treatment.* Regan gave a brief historical résumé of treatment from the alpha of amputation to the omega of ankylosis. Of supreme importance are early diagnosis and early *adequate* drainage. Repeated aspirations, drainage through small incisions, or aspiration with injection of antiseptics are usually inadequate in severe cases. Cases "cured" thereby are probably mild ones which would have recovered without surgical interference.<sup>160, 238</sup> Favorite methods of surgical drainage were described.<sup>9, 15, 160, 194, 238, 449</sup>

Patients are extremely toxic; transfusions, dietary care, relief from severe pain by narcotics are necessary.<sup>160</sup>

*Prognosis; Results of Treatment.* Prognosis is generally grave. Several factors determine the end result; results are better in the young than in those with joints traumatized by wear and age. Results are less satisfactory in hips (Regan) than in certain other joints. Some<sup>449</sup> say that results depend to a marked extent on the type of infection, that staphylococci produce ankyloses earlier and oftener than streptococci; others say just the opposite. The primary site of infection, not the germ, is the chief determining factor. The presence or absence of primary juxta-articular bone disease is the important factor in persistency of trouble.<sup>15, 160</sup>

Of equal or greater importance is the promptness with which the diagnosis is made and drainage instituted, for this determines the degree of damage to cartilage from proteolytic enzymes in pus.<sup>9, 238</sup> The only good results obtained by Regan occurred when treatment was instituted within the first six days of disease. Of Egger's patients, seven recovered some function, six developed ankylosis, two had amputations, one died of empyema. Of patients of Freiberg and Perlman, one retained good hip motion, three developed marked limitation, three ankylosis. Of the 113 patients of Badgley and associates seven retained normal function, 23 regained 50 per cent normal function, 83 developed irreparable articular damage with

numerous complications; of the latter 12 died of septicemia, two of post-operative complications.

*Experimental Embolic Staphylococcus Arthritis.* Kistler gave rabbits intravenous injections of (1) fully virulent, (2) partially sterilized, and (3) killed agglutinated and nonagglutinated saline suspensions of *Staphylococcus aureus*. Of the surviving animals that received living organisms, 100 per cent developed marked exudative arthritis with cartilaginous and osseous destruction; 53 per cent, endocarditis and suppurative pericarditis. Agglutinated and partly or almost completely sterile organisms produced even more marked and more chronic suppurative articular and subchondral lesions. Suspensions of completely sterile bacteria, whether agglutinated or not, produced no significant lesions.

#### RHEUMATIC FEVER

*Incidence.* Factors which govern the incidence of this disease pertain to geography and climate, season, economic factors, age and sex.

*Factor of Geography and Climate.* Nichol again summarized available data on the hospital incidence of rheumatic fever and of rheumatic carditis in various parts of the United States, from latitude 47° N. (Spokane) to latitude 25° N. (Miami). The data revealed a definite inequality in the distribution of the disease, the incidence being much less in the southern states. In West Virginia the acute stages of the disease are likely to be mild or absent but subsequent rheumatic carditis is common.<sup>519</sup>

In Nebraska the disease is common.<sup>544</sup> Christie noted that although the general incidence of rheumatic carditis was low, the hospital incidence among children in the San Francisco and University of California Hospitals was double or triple that of similar hospitals elsewhere in the country. This incidence cannot be blamed on the numerous health-immigrants to California since the incidence of rheumatic carditis is low in Los Angeles. Perhaps in northern California after an apparently typical onset and course the disease becomes "benign" and is not recognized in school examinations. In Wichita Falls, northern Texas, Whiting found the incidence of rheumatic fever and chorea to be  $\frac{1}{8}$  that of Virginia,  $\frac{1}{4}$  that of Boston.

(Since rheumatic carditis is more prevalent among those of lower economic strata may not his failure to include negroes have resulted in an artificially low incidence? —Ed.)

Physicians in the Mississippi Valley see about  $\frac{1}{6}$  as much rheumatic fever as those in New York, according to Kinsella.

Each year from 15,000 to 30,000 deaths from rheumatic carditis occur in England and Wales; 1500 in Ireland.<sup>371, 393</sup> In England and Wales 1 per cent of students entering, and 2.5 to 3 per cent of those leaving, urban elementary schools have rheumatic carditis and 1500 children under the age of 15 die therefrom each year.<sup>371</sup> In Ireland the incidence of rheumatic



fever varies from 1.03 per 1000 rural school population to 7.72 per 1000 urban school population. Statistics were presented on the incidence of juvenile rheumatic carditis in various cities of the British Isles.<sup>393, 455</sup> Carditis was five times as prevalent as tuberculosis in Glasgow and Edinburgh schools. One-third of all London children who were chronic invalids were crippled by rheumatism in some form.

Rheumatic carditis can no longer be considered a rare disease in India. According to Banerjea's statistics rheumatic fever is almost as common in South India and Bengal as in England and the United States. It is common also in the Bombay Deccan although not as prevalent as in other countries; of 100 cardiac cases in Miraj, 47 were rheumatic (Carruthers). Thus the percentage of heart disease of rheumatic origin was actually greater than elsewhere but the carditis tended to be less severe. Kar also noted the disease in India.

*Seasonal Incidence.* The disease was most prevalent in San Francisco in the first four months of the year<sup>85</sup>; in Minneapolis, in early spring and late fall.<sup>482</sup>

*Social and Hygienic Factors.* Most of the rheumatic children seen by Ash came from poor families. Eighty-three per cent were white; 17 per cent were negroes. The relative insusceptibility of negro children suggested that malnutrition and poverty are not sole contributing factors.

*Hereditary and Familial Factor.* Among 370 children studied by Shapiro were 201 with rheumatic carditis, 169 with nonrheumatic cardiac disorders. The incidence of rheumatic fever was three times as great in the families of the rheumatic group as in those of the nonrheumatic group.

Others noted a familial incidence of 32 per cent,<sup>85</sup> 24 per cent<sup>22</sup> and 18 per cent.<sup>197</sup>

*Factor of Age.* The disease may begin at any age but further statistics again indicated that it generally begins in persons before the age of 10, especially between five and seven years.<sup>11, 22, 80, 85, 197, 307, 455, 482, 568b</sup>

*Factor of Sex.* In the new American series the sex incidence as usual was slightly greater among females, the incidence in females being from 52 to 59 per cent.<sup>11, 85, 197</sup> Rheumatic chorea was much more common in females, Ash's ratio being 1 choreic boy: 2.5 girls.

The sex incidence was strongly reversed in the two series of cases from India. Seventy-seven per cent of Carruther's cases and 88 per cent of Banerjea's cases were in males. This may be due to the fact that especially in India women are more apt to be treated at home. Banerjea could not accept this idea because the relative preponderance of the disease in males prevailed in his private practice also.

#### GENERAL SYMPTOMATOLOGY AND PATHOLOGY OF RHEUMATIC FEVER

Swift's definition of rheumatic fever<sup>138</sup> affords a basis of understanding of its protean symptomatology. "Rheumatic fever is a disease of undeter-

mined etiology characterized by fever and a toxic state, and by the presence in certain organs of the body of small, disseminated focal lesions of a proliferative type. In acute stages there is also an exudation in and about the joints and sometimes in the pleura and pericardium. . . ." The term "*acute* rheumatic fever" has been widely objected to; in 1928 the American Heart Association dropped the use of the adjective "acute."

*Clinical Phases and Types.* According to Coburn and others there are three clinical phases in the development of an attack: (1) an acute upper respiratory infection lasting a few days; (2) the "silent phase" immediately thereafter with no clinical symptoms and signs—it lasts for a few days to six weeks, generally one or two weeks; (3) the attack phase—the period of rheumatic manifestations varying widely in intensity and duration. Subsequently the disease runs any one of three courses: monocyclic, polycyclic or continuous.<sup>188</sup>

*Histopathologic Reaction Underlying Symptoms.* Swift and Derick again described the two basic inflammatory reactions, knowledge of which is so helpful in understanding the symptoms and pathology of the disease.

Two different pathologic reactions occur, exudation and proliferation; both are tissue responses to injury. An exudative reaction provides, for example, the acutely swollen joint; the proliferative reaction produces subcutaneous nodules and the myocardial Aschoff body. The two reactions are not mutually exclusive; often they coexist. The exudate consists of plasma or of synovial fluid and wandering cells; this reaction is earlier and more evanescent than the proliferative reaction. The latter appears later and is more lasting. Cells comprising the proliferative reaction are apparently not phagocytes, nor are they the epithelioid cells seen in tuberculosis or syphilis. Primitive cells, they arise from resting mesenchymal cells or from endothelial elements. Their peculiar arrangement as submiliary nodules is specific for the disease, according to some, nonspecific according to others.<sup>532</sup>

Klinge (1933) recently emphasized another feature which he believes precedes and is responsible for the proliferative tissue reaction; namely, an alteration in the intercellular mesenchymal substance demonstrated by evidences of injury to collagen fibers varying from simple focal edema to fibrinoid swelling and focal necrosis. The cause of the fibrinoid swelling is unknown. Such changes can be induced by bacteria or bacterial toxins but not by viruses. Fibrinoid swelling is also present in experimental scurvy. Thus, it is not a specific reaction. It may be a manifestation of tissue hyperergy; Klinge noted it in tissues of rabbits repeatedly injected with foreign protein.

#### SPECIAL CLINICO-PATHOLOGIC DATA CONCERNING RHEUMATIC FEVER

*Incidence of Various Symptoms.* In Ash's 416 cases the initial symptom was febrile polyarthritis in 58 per cent, chorea in 21 per cent, carditis in 17 per cent. In Christie's 116 cases the initial symptom was arthritis in 68 per cent, chorea in 28 per cent, carditis in 21 per cent, tonsillitis in 19 per cent, nodules in 10 per cent, other symptoms less frequently. Among the 73

cases of Gibson and Denenholz the initial symptom was arthritis in 57 per cent, carditis in 35 per cent, chorea in 8 per cent. In adults, polyarthritis is a more common feature than carditis but in children the reverse is true; a child may have only one or no joints affected (Derick).

*Joints.* Articular symptoms were present some time during the disease in from 58 to 76 per cent of new cases reported<sup>11, 85, 197</sup> including those from India.<sup>22, 80</sup> Rarely the arthritis of rheumatic fever may be so persistent and marked as to simulate acute arthritis deformans.<sup>532</sup> Generally articular symptoms were transient; chronic arthritis was practically never produced. "Rheumatic fever always discards its articular features eventually" (Kinsella).

Most "growing pains" and leg aches in children are not rheumatic, according to Shapiro who again differentiated between the rheumatic and non-rheumatic variety.<sup>247, 482</sup>

*Heart.* Statistics on the incidence and type of cardiac disease in the current cases conformed to previous data.<sup>11, 65, 197, 307, 482, 572, 577</sup> Although the heart is practically always affected, the cardiac damage does not persist in all cases and Derick often noted disappearance of disturbances of conduction time. "The heart is frequently spared in the first attack, rarely in the second, probably never thereafter." Of Banerjea's patients in India 12 per cent had "active carditis," 60 per cent had mitral stenosis, 8 per cent had aortic insufficiency, 12 per cent had mitral stenosis and insufficiency, and in one case (4 per cent) mitral and aortic stenosis and aortic insufficiency were present. According to Carruthers, multiple valvulitis is distinctly less common in India than in the United States. But the percentage of cases of rheumatic carditis with no previous history of rheumatic fever was no greater in the Bombay Deccan than elsewhere. Therefore Carruthers could not agree with McLean (1932) that there is a greater incidence of rheumatic carditis without rheumatic fever in the South.

Some cardiologists state that organic mitral regurgitation is rare and never causes serious disability, and that high grades of mitral disease always involve mitral stenosis. However, according to Dana and Reidy pure mitral regurgitation is not uncommon, occurs in 20 to 50 per cent of all cases of rheumatic mitral valvulitis, and it alone can cause death, uncomplicated by disease of other valves or by pericarditis. Pure mitral stenosis is rarely found at necropsy and its clinical importance is much overemphasized. Contrary to the belief of some, rheumatic fever does not predispose to arteriosclerotic coronary disease in later life, according to Gross and Oppenheimer.

Acute rheumatic myocarditis is one of the rare causes of sudden death. Not preceded by a history of rheumatic fever or carditis, it caused the sudden death of a 59 year old woman in whose heart Mallory found more Aschoff bodies per cu. mm. than he had ever seen before. Studies on the pathology of valves, valve rings and the auriculoventricular conduction system in rheumatic fever were reported.<sup>196, 215, 216, 217</sup>

*Pericardium.* Clinical signs of acute pericarditis were noted in 12 per cent of cases,<sup>11, 85</sup> 14 per cent<sup>455</sup> and 19 per cent.<sup>138</sup> Other data on rheumatic pericarditis were reported.<sup>188, 197</sup> Rheumatic fever rarely causes significant pericardial effusions; "only an examination candidate revels in paracentesis pericardii."<sup>197, 498, 499</sup>

*Lungs.* Rheumatic pneumonia occurred in 7.6 per cent of Ash's 416 rheumatic children, appearing only in those severely affected. Bronchopneumonia or lobar pneumonia may occur at any stage of the disease, according to Willius. Poynton listed four types of pulmonary complications: 1. Massive collapse may occur, usually on the left, sometimes on both sides. It is early manifested by intense tubular breathing at the lower angle of the scapula, which then spreads downward. When classic it has no other adventitious signs and will appear, disappear, reappear and disappear. 2. Bronchopneumonia may appear alone or may complicate massive collapse. 3. Pleural effusion may appear and necessitate paracentesis. 4. Acute edema of lungs—sharp, bright crepitations commencing in upper lobes—was noted by Poynton only in patients receiving large doses of salicylates. Mallory stated, "So far I have no clear conception as to whether there is a rheumatic pneumonia entity. . . . I cannot make head or tail of the descriptions." Noted by him were multiple focal areas of hemorrhage through one lung, looking much like infarcts but usually not leading to complete necrosis of lung tissue; also microscopic lesions were seen in some of the very small pulmonary arteries near hemorrhagic foci. Histologically the lesions were "about half-way between infarcts and pneumonia in appearance."

*Chorea (as a Symptom).* Chorea was noted in 5 to 34 per cent of current American cases<sup>11, 85, 197, 572</sup> but in very few of those seen in India.<sup>22, 80</sup>

*Nodules.* Subcutaneous nodules were noted in 2.4 per cent of Ash's cases, in 8 per cent of Banerjea's cases, but in 37 per cent of the fatal cases of Gibson and Denenholz. Not all "fibrous nodules" are actually fibrous: some can appear and disappear within three days. Rheumatic nodules have three zones: an outer one of swollen fibrous tissue containing distended capillaries, a middle one full of leukocytes and mononuclear cells and a central zone of necrosis (Poynton).

*Abdominal Symptoms.* Writers are stressing the fact that abdominal pains may be one of the rheumatic symptoms. They occurred in 13 per cent of Ash's 416 cases; in three cases symptoms warranted surgical operation; only acute generalized mesenteric lymphadenitis was found. (However in three others intercurrent acute appendicitis was found at operation.) Wolffe and Brim reviewed the literature thereon, reported three such cases, and summarized the features of these and other cases.

The gastrointestinal inflammation produces recurring spells of abdominal cramps. Attacks may be acute or chronic. When acute, the cramps may last a few minutes or a few hours. The pains are sharp, sometimes about the umbilicus, sometimes generalized, but usually epigastric and not radiating. Nausea may be present, occasionally vomiting. Abdominal tenderness may or may not be present; rigidity

is absent. An episode is usually over before the next meal and the child generally continues to eat and play. Constipation is generally present, also slight fever, rarely over 101° F. There may be a history of slight nose bleeds or of pains in muscles and joints, or the cramps may be the only subjective rheumatic manifestation. Attacks may recur over a period of six months to several years. If the condition is chronic the patient notes mild attacks of fleeting abdominal pain from time to time without other signs or symptoms except occasionally diarrhea alternating with constipation. Unlike appendicitis, successive attacks become milder.

*Laboratory Data (Electrocardiograms, Sedimentation Rates, Blood Counts, Urinary Studies).* The practical value of the electrocardiographic Lead IV is "definitely limited" according to Robinow, Katz and Bohning who studied results in normals, in children and in adults with active and inactive rheumatic fever.

*Erythrocyte Sedimentation Rate.* The close relationship between rheumatic activity and altered sedimentation rates received further notice. The test allows accurate observations on the progress of the disease but other conditions which alter the test must be known. According to Payne and Schlesinger the rate is not altered by an uncomplicated common cold or by "chronic" tonsillar infection but is notably altered by acute tonsillitis and influenza. In acute chorea there is no, or only a small, transient, increase of rate. Congestive cardiac failure has a curious effect on the rate; however active the rheumatic process may be, the onset of congestive failure and edema causes the rate to fall from a previous high figure, sometimes to normal. Such a fall in the presence of active disease is a bad prognostic sign. When nodules are present the test has prognostic significance; a fall of the rate heralds their disappearance. "Miniature rheumatic fever" is characterized by slight fever and transient tachycardia. Such a state, precipitated by tonsillitis or respiratory infection, may be subclinical but is indicated by changes in the rate.

To determine the mechanism of production of increased rates Coburn and Kapp studied changes in rate occurring in the three phases of a rheumatic attack: the pharyngitis or respiratory infection, the silent phase, and the phase of attack. In rheumatic patients who did not develop an exacerbation after pharyngitis, sedimentation rates were either not or very slightly and briefly (for 10 to 15 days) altered, but in those in whom pharyngitis precipitated a rheumatic exacerbation the rate suddenly rose to a high level late in the "silent" phase just before "the attack." By varying the concentrations of plasma protein Coburn and Kapp determined that increased rates in acute rheumatism are caused by an increase in plasma fibrinogen and globulin.

Removal of total serum lipoids and crystalloids did not appreciably affect the rate. Dilution of plasma with Ringer's solution slowed the rate as did removal of fibrinogen. Removal of globulin and fibrinogen inhibited rates almost completely. Adding globulin, but especially fibrinogen, increased the rates. The globulin and fibrinogen in blood of rheumatic patients was qualitatively the same as that in normal blood. It was suggested that fibrinogen and globulin are produced by the reticulo-endothelial system.



*Blood Counts.* The behavior of eosinophilic polymorphonuclear leukocytes in rheumatic fever is similar to that seen in other infections. Friedman and Holtz noted that eosinophiles are absent or diminished in number during the height of acute rheumatic polyarthritis and carditis, and reappear during the stage of recovery, so that there is a postinfectious eosinophilia as in other infections. Long continued aneosinophilia and hypo-eosinophilia during acute polyarthritis or during acute or chronic carditis indicate intensely active infection. Recurrent and continuous eosinophilia indicates convalescence.

The sedimentation rate is a more sensitive and practical index of rheumatic activity or inactivity than the Schilling count (Struthers and Bacal; Rogatz). In the acute stage there is a marked shift to the left in the Schilling hemogram; that is, the percentage of immature polymorphonuclear leukocytes rises above 10. As the disease becomes inactive the shift returns to normal with, or often two or more weeks before, the sedimentation rate. Patients should not be allowed up until the sedimentation rate is normal.

*Synovial Cytology.* Sterile fluid from a synovial effusion of one febrile rheumatic patient contained 7200 total cells per cu. mm. with 92 per cent polymorphonuclears.<sup>93</sup>

*Urine.* Coproporphyrin in abnormal amounts was found by Kapp and Coburn in the urine of patients with acute rheumatic fever, concurrently with onset of symptoms. Normal amounts were found in the urine of patients with inactive rheumatism. Its appearance bore no relationship to fever, hematuria or therapy, and probably indicated some kind of hepatic damage.

#### RELATIONSHIP OF RHEUMATIC FEVER TO OTHER DISEASES

*To Subacute Bacterial Endocarditis.* Reports under review contained no new comments on this point. Death from subacute bacterial endocarditis occurred in a few cases.<sup>455, 482, 572</sup>

*To Atrophic Arthritis.* Most physicians believe that rheumatic fever and atrophic arthritis are not manifestations of the same disease and bear little or no relationship to each other.<sup>8, 271</sup> In the United States acute atrophic arthritis practically always leaves persistent articular damage; rheumatic fever "always discards its articular features."<sup>307</sup> Although Cecil did not regard the two as the same disease he thought they might be related etiologically. Dawson and Tyson considered them closely related, differing in degree rather than in kind. According to them rheumatic fever and atrophic arthritis tend to occur in the same families. Each disease appeared with almost equal frequency (14 and 15 per cent respectively) in the families of 100 patients with atrophic arthritis. They considered the geographic, age and seasonal incidence and the precipitating factors, to be about the same in both. Subcutaneous nodules of "very similar nature" appear in both.

(We do not believe they are similar.—Ed.)

However, immunologic differences obtain: in rheumatic fever anti-streptolysins are high, streptococcal agglutinins are not; in atrophic arthritis the reverse occurs. Even so hemolytic streptococci may play a rôle in both diseases. But even were both caused by the same agent they could be different diseases; witness the relationship between syphilis and yaws. Although the two diseases may represent different responses to the same or closely related agents, Dawson and Tyson stressed the importance of differentiating them clinically, for each has its own symptoms, therapy and prognosis.

(Too much credence cannot be given statements that both diseases are rare in the tropics. Statistics published elsewhere<sup>247</sup> and herein tend to refute this idea. If the differences between the two diseases depend largely on age, one should not so frequently see Still's disease (juvenile atrophic arthritis) in children or an initial attack of classical rheumatic fever in adults more than 40 or 50 years of age.—Ed.)

*Differential Diagnosis.* Kinsella and Archer reviewed the usual points which differentiate the disease from Still's disease, acute atrophic arthritis, gonorrheal arthritis and gout. Annually there are reported one or two cases of leukemia simulating acute rheumatism, presenting fever and joint pains. Conybeare reported such a case.

*Course and Prognosis.* "As the heart goes so goes the disease" is a timely but truthful paraphrase. The principal cause of heart failure is not physical strain but continued infection, in particular the prolonged activity of the rheumatic infection, according to Werner. Respiratory infections lowered the cardiac reserve of 50 per cent of Werner's patients with rheumatic carditis but also of the same percentage of those with syphilitic carditis. The rôle of respiratory infections therefore seemed to be nonspecific.

*Effect of Pregnancy.* Pregnancy coincident with heart disease is serious for both mother and child; the maternal mortality is high (3 to 8 per cent); premature birth is frequent. At least 1000 women are said to die annually in the United States from heart disease complicating pregnancy and 90 per cent of the carditis is rheumatic. The maternal mortality in the Toronto General Hospital under such circumstances was 2.3 to 3.4 per cent. Henderson changed the regimen with the result that in a new series of 35 deliveries 46 per cent were spontaneous, 51 per cent were by forceps, 3 per cent only were by cesarean section and sterilization. One patient died from heart failure. Premature birth occurred in seven cases (20 per cent). Once cardiac insufficiency has occurred the maternal mortality is more than doubled; if labor occurs during cardiac failure the mortality is about 50 per cent. Henderson recorded his prenatal regimen, indications for termination of pregnancy and for sterilization, also his management of the various stages of labor.

*Recurrences.* The mechanism underlying relapse is not understood. Poynton and Swift asked: Are they caused by the introduction of fresh infection from some distant focus into susceptible subjects, by some sudden

failure in resistance before the infection is thoroughly destroyed, by some fresh revival of the virulence of the infection which is passing through a phase in its life history? Are they caused by an altered reactivity of tissue so conditioned that slight insults of various types lead to a peculiar mode of response, or by the prolonged residence of some infectious agent in the rheumatic subject, with alternate periods of almost complete immunity and then of diminished resistance?

In 52 per cent of Shapiro's 342 cases of juvenile rheumatism only one attack was experienced; the rest of the patients had recurrences, 54 per cent of them within two years, 17 per cent in the third year, 12 per cent in the fourth year, 3 per cent in the fifth year and 14 per cent thereafter. Until five years have elapsed a patient cannot be too hopeful of escaping a recurrence.

*Evidence of Reactivity and Quiescence.* Ruprecht's criteria of "arrest" included disappearance of subjective signs and symptoms, and normal values for the following: temperature, leukocyte count, Schilling hemogram, nonfilament count and sedimentation rate. Sutton and Dodge gave their criteria for a diagnosis of active carditis.

Bland, Jones and White observed 1000 young patients with rheumatic carditis for 10 years. There was a regression in physical signs in many, a total disappearance of clinical signs of carditis in 83 cases (8.3 per cent).

*End Results.* Twenty-two per cent of Ash's patients with juvenile rheumatism were dead after an average of 7.5 years, and 10 per cent of Shapiro's patients were dead after an average of 6 years of illness. Lesions noted at necropsy were recorded. Banerjea's figures on the mortality of the disease in India agreed with those of Lewis (1933) in England. Relapses occurred in 40 per cent; death occurred within two years in 4 per cent, within 10 years in 24 per cent. Willius' 160 cases, studied until death, included adults; at death 78 per cent had mitral disease, 13 per cent aortic, and 9 per cent both mitral and aortic disease. The first two groups lived an average of 21 years, the third group 16 years after the disease's onset. The disease was rapidly fatal among the Chicago children observed by Gibson and Denenholz; in 40 per cent the first attack of carditis proved fatal. The average age at onset of the disease was 6.3 years; its average duration until death, only 1.4 years. Twenty-seven per cent died within three months of their first rheumatic manifestation.

#### ETIOLOGY AND PATHOGENESIS OF RHEUMATIC FEVER

*Factor of Infection.* Direct and indirect bacteriologic evidence for the infectious theory were summarized by several (table 1).<sup>447, 532</sup>

1. *Respiratory Infections.* The majority now consider the prodromal respiratory infections to be nonspecific provocatives. Among Shapiro's cases the disease appeared spontaneously in 45 per cent, was preceded by colds in 14 per cent, by a sore throat in 5 per cent, by other factors in 36

TABLE I

Immunologic and Chemical Differences between Rheumatic Fever, Atrophic (Rheumatoid) Arthritis and Hypertrophic (Osteo-) Arthritis \*

Test	In normal persons (or other controls)	In rheumatic fever	In atrophic (rheumatoid) arthritis	In hyper- trophic (osteo-) arthritis	Comment: significance of test
Skin reactions to streptococci nucleoproteins of Green streptococci	Occasionally + (in 20-40 per cent) Occasionally + (in 20 per cent or less)	Generally + (in 75-80 per cent) Occasionally + (in 20 per cent or less)	Generally + (in 75-95 per cent). Maximal reactions common. Occasionally +. Maximal reactions rare	Generally - Occasionally + Generally -	Significance debatable. Positive much more frequently to hemolytic than to green streptococci. Not strain specific. No definite correlation between skin reactions and agglutination test.
Agglutinins to	Hemolytic streptococci	Rarely +. Occasionally + in non-rheumatic patients	+ in some cases (25 to 50 per cent)	Practically always -. Rarely +	Significance debatable. Reactions are to several, not to one, strain. No correlation between agglutination tests and the duration, extent, or severity of patient's arthritis. Presence of such agglutinins may be attributable to natural rather than to acquired or specific immunity
	<i>Streptococcus viridans</i>	Rarely + (in about 5 per cent)	Rarely + (in 5-10 per cent)	Generally - Rarely +	
Precipitin reactions to fractions of hemolytic streptococci	Generally none or very few. Occasionally present in nonrheumatic patients with recent tonsillitis	In about 60 per cent of active cases +. In quiescent cases, generally "negative"	+ in 80 per cent of cases (group, not strain, specific)	Rarely + (in 10-20 per cent)	Close approximation, but not an absolute agreement, between precipitin and agglutination reactions. In rheumatic fever no constant relationship between severity of symptoms and presence of precipitins. Precipitin reaction (to hemolytic streptococci) frequently + in various types of arthritis, even gonorrheal

\* Figures given are from the recent literature. Normal standards in some instances not yet finally established; contradictory results are frequently noted.

TABLE I—Continued

Test	In normal persons (or other controls)	In rheumatic fever	In atrophic (rheumatoid) arthritis	In hypertrophic (osteoarthritis)	Comment: significance of test
Antifibrinolysins (to hemolytic streptococci)	Present in small amounts. Present in certain amounts in those without evidence of recent hemolytic streptococcal infections. Much increased in erysipelas and other acute hemolytic streptococcal infections	Much increased in 60–70 per cent	Generally not present. Occasionally present in cases of early acute arthritis. Rarely present in chronic cases		Antifibrinolysins and antistreptolysins are indexes of recent acute hemolytic streptococcal infection. Their presence should not be expected in chronic disease.
Antistreptohemolysins "antistreptolysins" "antihemolysins" "anhemolysins"	Usually up to 50–100 units. Rarely over 150 units. Occasionally up to 200–300 units	In about 80–85 per cent of active cases increased markedly (average 500 units). In quiescent cases may not be increased	Only increased (over 150 units) in about 10–20 per cent of cases. Later generally not increased	Normal	Significance of antistreptolysins debatable; some say they may be increased in patients with respiratory infections from other than hemolytic streptococci. No relation between antistreptolysin titer and agglutination or skin reactions
Streptococcal Complement-fixation test	Sometimes + even in pregnancy and tuberculosis	In active cases sometimes +. In quiescent cases only occasionally +	Usually – according to some, usually + according to others		Significance very debatable. Patients may show complement fixation, not only to several strains of streptococci, but also to staphylococci and colon bacilli
Sedimentation rate	Generally below 15 mm. (in 1 hour)	Markedly increased. May return to normal in cases of congestive heart failure	Almost always increased generally over 30 mm. (1 hour)	Rarely over 20 mm. (1 hour)	



TABLE I—Continued

Test	In normal persons (or other controls)	In rheumatic fever	In atrophic (rheumatoid) arthritis	In hyper- trophic (osteo-) arthritis	Comment: significance of test
Total blood proteins	6-8 gm. per 100 c.c.		Normal	Normal	
Plasma fibrinogen	300-600 mg. per 100 c.c.		Increased	Normal	
Serum globulin	1.2-2.3 gm. per 100 c.c.	Increased	Increased	Normal	Tends to rise in infectious diseases
Serum albumin	4.6-6.7 gm. per 100 c.c.	Decreased	Decreased	Normal, or slightly de- creased	
Albumin-globulin ratio	1.5 : 1 to 3 : 1		Frequently below 1. Tends to become nor- mal as patient re- covers	Normal	
Serum calcium	9-11 mg. per 100 c.c.		Normal	Tends to be slightly de- creased	
Plasma cholesterol	160-230 mg. per 100 c.c.		Tends to be decreased	Tends to be in- creased	Tends to fall in infectious diseases, rise in "metabolic diseases."

per cent. About 50 per cent of the patients of Gibson and Denenholz noted no prodromal respiratory infections. According to Swift, severe pharyngitis or tonsillitis of apparent hemolytic streptococcal origin produces rheumatic relapses in 50 to 60 per cent of previously rheumatic subjects but produces rheumatic symptoms in less than 10 per cent of nonrheumatic subjects. The disease has been precipitated by measles, other exanthems, antismallpox vaccination, injuries, surgical operations, foreign-protein (typhoid) reactions.

2. *Blood Cultures.* Blood cultures made by McEwen, Alexander and Bunim on 90 patients with febrile rheumatic polyarthritides were sterile in 83 per cent of cases, positive in 17 per cent; hemolytic streptococci were found in 3 per cent, green-producing streptococci in 13 per cent, indifferent streptococci in 1 per cent. Comparing results with those in normal and pathologic controls, they concluded that streptococci cannot be isolated from the blood in rheumatic fever (or in atrophic or other arthritides) more frequently than in miscellaneous diseases. Streptococci recovered in rheumatic fever did not differ from those in atrophic arthritis. Organisms recovered were probably of no etiologic significance. If large quantities of blood and suitable methods are used, streptococci occasionally can be isolated from the blood even of normal persons, but more frequently from those whose resistance is lowered by chronic illness. Meyer and Ryan cultured the blood of normal and of rheumatic children, using Kendall's medium, a modification of Clawson's method, and serial transfer technic. Insignificant bacteria, mostly diphtheroids, were occasionally obtained from patients and controls. All specimens would have been considered sterile by usual methods.

Cecil does not believe that the bacteria previously recovered by him were contaminants; too many workers have found them in blood, but their significance is admittedly undetermined. Poynton warned that results of cultures of tissues and exudates must be interpreted carefully. Unlike suppurative processes that may burst into joints, rheumatic processes do not pour streptococci into fluids. As one is not surprised by negative cultures in gonorrheal or tuberculous arthritis, so one should anticipate negative cultures in rheumatic fever.

3. *Skin Tests.* Positive skin reactions to hemolytic streptococci were noted by Wasson in 79 per cent of 137 ambulatory rheumatic children, in 29 per cent of nonrheumatic controls. There was no relation between the intensity of the skin reaction and the degree of carditis. The frequency of positive tests increased with the children's age. Retesting showed considerable variability in skin tests on the same patient, due to differences in their general and rheumatic condition.

Goldie and Griffiths noted positive skin reactions to hemolytic (but not to green-producing) streptococci three times as often in rheumatic patients as in controls. Tests were positive in 77 per cent of 85 cases of rheumatic fever (and in 24 per cent of controls) tested with a concentrated solution of hemolytic streptococci; in 34 per cent of 154 cases (but in no controls)

tested with a less concentrated solution. However, skin tests were generally negative in patients with severely progressive rheumatic fever (as patients with miliary tuberculosis may have negative tuberculin tests). Tests with green-producing streptococci were positive in only 27 per cent of 60 rheumatic patients (and in 24 per cent of controls) with a concentrated solution, and in 3 per cent each of 154 rheumatic cases and 30 controls with a less concentrated solution.

4. *Streptococcal Agglutinins.* Positive agglutination tests with hemolytic streptococci (titer 1 to 20 or over) were found by McEwen, Alexander and Bunim in none of 35 normal controls, in only 5 of 71 patients with rheumatic fever (titer 1 to 20 in one, 1 to 40 in two, 1 to 80 in three). Thus these workers did not confirm Coburn and Pauli's observation (1932) that serum of most patients with acute rheumatic fever agglutinated hemolytic streptococci to a titer of 1:10 to 1:40. Goldie and Griffith found agglutinins to hemolytic streptococci in a titer of 1:100 in 80 per cent of rheumatic fever patients, in 10 per cent of controls; agglutinins to green-producing streptococci in a titer of 1:100 in only 6 per cent of rheumatic cases, in 5 per cent of controls.

5. *Antifibrinolysins.* Patients convalescing from diseases due to hemolytic streptococci generally possess antifibrinolysins; that is, the fibrin in their sera is markedly or completely resistant to fibrinolysis, or liquefaction of blood clot, by cultures of hemolytic streptococci. Confirming the work of others<sup>245, 246, 247</sup> Stuart-Harris noted antifibrinolysins in the blood of patients with rheumatic fever (but not with atrophic arthritis) particularly during the acute stage or after intercurrent streptococcal infection during convalescence from activity. Thus he considered rheumatic fever (but not atrophic arthritis) related to hemolytic streptococcal infection. The findings of McEwen, Alexander and Bunim were similar, complete resistance to dissolution being noted in 59 per cent, marked resistance in 14 per cent, of 29 patients with rheumatic fever.

6. *Hemolytic Streptococcal Precipitation Tests.* Antigenically hemolytic streptococci are complex mosaics containing, among other fractions, a "nucleoprotein" (P fraction) which is not specific as it gives cross precipitation with other gram-positive cocci, a group-specific carbohydrate (C fraction), and type-specific protein and carbohydrate fractions (M and S fractions). Hemolytic streptococci are known to induce the formation, not only of antistreptolysins and antifibrinolysins, but also of two other antibodies, anti-C precipitins and anti-P precipitins. These four antibodies have been demonstrated in the serum of patients with various streptococcal infections. Because they have also been found by some workers in a high proportion of patients with rheumatic fever it has been suggested that there is a close connection between streptococcal infection and this disease. McEwen, Alexander and Bunim, and Chasis and McEwen noted precipitin reactions to crude "C" extracts (fractions) in 56 per cent of 39 patients with rheumatic fever but also in a fairly high percentage of patients with

other articular diseases and in 24 per cent of normal controls. Highly positive reactions were noted equally in those with rheumatic fever or with atrophic arthritis, less frequently in controls. The test therefore was of no differentiating value, an opinion concurred in by Race.

Swift and Hodge studied the development of type-specific anti-M precipitins in two groups of patients suffering with hemolytic streptococcal infections. Most of the patients in group I, none of whom developed rheumatic fever, showed relatively strong type-specific reactions in their serum within four to five weeks. Those in group II all developed rheumatic fever; some had similar strong antibodies early, but most rheumatic patients from whom hemolytic streptococci were cultured in significant numbers from various foci, did not show strong anti-M precipitins until distinctly later than the nonrheumatic group. Swift has repeatedly been unable to show a constant relationship between the severity of symptoms of patients with rheumatic fever and the presence of precipitins against either the "C" (carbohydrate) or the "P" (nucleoprotein) fractions of group A hemolytic streptococci.

7. *Antistreptolysins* ("Antihemolysins": "*Anhemolysins*"). The upper limit of normal was regarded by earlier workers to be 50 units of antistreptolysin, by later workers to be 150 units.<sup>245, 246, 247</sup> The establishment of the new level made the test more specific but at the cost of reporting "normal values" in 24 to 30 per cent of cases of rheumatic fever, with titers between 50 and 150. Race believes the upper normal level should be re-established at 50 units. Eighty per cent of 51 rheumatic fever patients (but only 3 per cent of 37 normal controls and 12 per cent of patients with atrophic arthritis) showed 150 or more units of antistreptolysin, according to McEwen and colleagues. However, the titer did not rise above 25 units in one unquestionable case studied over two months. Goldie and Griffiths noted "abnormal values" (over 50 units) in 100 per cent of 40 cases of "rheumatic fever with chorea," in 88 per cent of 154 cases of subacute rheumatism, in 20 to 27 per cent of two sets of controls. Values of 100 + units were found in 92 per cent, 58 per cent and 3 to 8 per cent respectively; 200 + units in 80 per cent, 35 per cent and 0 to 2 per cent respectively. Longcope regarded 100 units as the limit of normality. The antistreptolysin titer was above 100 units in 85 per cent of his cases of acute rheumatic fever, in 86 per cent of cases of chorea, in 80 per cent of cases of erythema multiforme and nodosum, in 28 per cent of cases of "chronic inactive rheumatic heart disease," in 46 per cent of cases of atrophic arthritis. It was over 200 units in 51 per cent, 50 per cent, 60 per cent, 0 per cent and 18 per cent of these same groups respectively. Contrary to the experience of Coburn and Pauli (1935), in Longcope's series the height of the titers did not parallel the severity or duration of acute attacks of rheumatic fever. High titers in this disease should be regarded as the result of a recent hemolytic streptococcal infection but "cannot be used as evidence that [rheumatic fever] is caused by hemolytic streptococci."

*Correlation and Interpretation of Immunologic Data.* The significance

of these data is incompletely understood (table 1). Little has occurred to change the interpretation of the main features as given in the third review. Space does not permit the inclusion of reported explanations of the conflicting data and reference must be made to the reports cited. Coburn's correlation still seems the clearest; whether correct or not it is the most positively stated. It seems to do much to explain the basis for the conflicting opinions (for example, that of Coburn and Wilson) reported in previous reviews. It attempts to show why some pharyngeal infections never produce initial or subsequent rheumatic attacks, why some hemolytic streptococcal infections sometimes do and sometimes do not (even in rheumatic subjects) produce attacks, and why rheumatic attacks are generally but not always precipitated in susceptible individuals with the production of antistreptolysins.

To clarify the mechanism of its production one must divide the rheumatic process into its three clinical phases which, although symptomatically distinct, are interdependent stages of a specific set of immunologic reactions. Each phase must be considered separately, yet sequentially. The first phase, that of acute upper respiratory tract infection, lasts only a few days. But in this phase are set in motion factors which may or may not eventuate in the rheumatic explosion. The second phase follows immediately after the respiratory infection, is characterized by a complete absence of clinical symptoms and signs, and lasts from a few days to about six weeks, generally one to two weeks. Although this phase is symptomless it is crucial, for during it, processes initiated in the first phase come to maturity; if they mature in one way, normally as they usually do, a rheumatic attack does not materialize, but if they mature in another way, abnormally, a rheumatic attack of variable severity results. The third phase begins with the onset of rheumatic manifestations and varies widely in the duration and intensity of its symptoms.

The hemolytic streptococcal infection (pharyngitis) of phase one is nonspecific in at least certain ways; the rheumatic patient is no more or less susceptible to it than the nonrheumatic patient. The clinical characteristics of the pharyngitis are the same in the rheumatic and the nonrheumatic; the upper respiratory tract of the rheumatic patient may be infected with the same strains of hemolytic streptococci as that of the nonrheumatic; and the pharyngeal infection has the same variable persistency in the nonrheumatic as in the rheumatic patient. Why then does one patient get acute rheumatism and the other not? A crucial difference lies in the type of immune response which the infection generates; furthermore, the chief difference in type is not just a difference in the content of the immune response but in the speed of its development. If an immune reaction to the phase-one infection fails to develop (as it may in either the rheumatic or nonrheumatic patient) or if it develops in the second or silent phase, with normal promptness, no rheumatism results in the normal person or even in one previously rheumatic, and the third phase never materializes. But if an immune reaction, engendered by phase one, develops tardily in phase two, with abnormal slowness, then rheumatic fever results. The basis of this concept follows:

The potent types of pharyngitis (as far as the production of rheumatic fever is concerned) are commonly due to hemolytic streptococci, Lancefield group A. As they pertain to rheumatic fever they are group but not strain specific. These hemolytic streptococci produce two or more soluble antigens (soluble bacterial derivatives or exotoxins) and at least three other antigens (intracellular bacterial derivatives or endotoxins). The two well-recognized soluble antigens are (1) an erythrogenic toxin, probably capable of damaging vascular endothelium and against which the



body generally forms neutralizing antibodies which cause the patient to be "Dick-negative," and (2) streptolysin which the body attacks by the production of anti-streptolysins—antibodies which are specific for hemolytic streptococci, probably group specific, which are quantitatively measurable by titration and which are recognized as bona fide evidences of recent hemolytic streptococcal infection.

The three other recognized antigens (intracellular bacterial derivatives) produced by hemolytic streptococci are (1) a type-specific protein, called M-substance or M-extract, against which the body during a rheumatic attack forms "precipitins to M-substance" which can be detected qualitatively in serum, (2) a nucleoprotein called P-substance, against which the patient's body frequently develops "precipitins to P-substance," the presence of which is demonstrated by positive skin reactions to hemolytic streptococcal nucleoprotein, and (3) a group-specific carbohydrate or C-substance, precipitins to which the patient's body develops and delivers to serum.

Still another protective substance found in the blood of patients with rheumatic fever or with definite hemolytic streptococcal infections is antifibrinolysin.

The relative importance of these antigenic substances and what pathologic reactions they induce or could induce in the body were they not neutralized by antibodies has not been fully determined. It appears, as one might expect, that erythrogenic toxin and streptolysin are released at the onset of infection whereas the M-substance and nucleoproteic P-substance are liberated after the disintegration of bacterial cells. According to Coburn the antistreptolysin curve (its quantity and speed of development) shows the patient's response to infection. He feels that an understanding of the abnormal response may help to elucidate the mechanism of an attack.

The silent phase two varies considerably in length but its duration appears to coincide with the time required for the appearance of the antistreptolysin response in rheumatic patients. Coburn noted previously that in a group of rheumatic subjects infected with a single strain of hemolytic streptococcus those that developed acute rheumatism developed an antistreptolysin response, while those who failed to make this response escaped an attack. He noted that a rheumatic patient who contracts a series of hemolytic streptococcal infections develops acute rheumatism only when the infection is followed by a rise in antistreptolysin titer. In the absence of an antistreptolysin response there was no rheumatic attack. He then studied the comparative alterations in the erythrocyte sedimentation rate and the antistreptolysin titer in 100 patients with rheumatic carditis in relation to different stages of phase three.

At the onset of symptoms the sedimentation rate and antistreptolysin titer both rise; at the height of the attack the rate is at its maximum but the titers still rise. When symptoms begin to subside the rate is still at its maximum, the titer is either at its maximum or still continues to rise. As symptoms continue to subside the rate falls but there is a lag in the fall of the titer; the titer may stay at its maximum or start to fall. When the rheumatic process has become quiescent the rate is normal, the titer may still be elevated but is falling, or may have reached normal. Thus the initial symptoms appeared with the appearance of the antibody but the curve of subsequent symptoms did not parallel the antibody titer.

After different hemolytic streptococcal infections the time when the maximum concentration of antistreptolysins occurs varies widely. In acute rheumatism maximum titers rarely occur within five weeks; in protracted cases they are not usually reached until several months after the hemolytic streptococcal pharyngitis. This is in sharp contrast to what obtains in erysipelas, for example, where the peak-titer is reached within 20 days after the onset of infection. Coburn found that the clinical character of the rheumatic attack varied with the shape of the antistreptolysin curve. The sooner a patient developed a maximal titer, the sooner he recovered. In other words those curves which approached normal responses (an early rise and fall) were

associated with short or mild attacks. In contrast, those characterized by an abnormally slow rise were associated with a prolonged severe carditis. Apparently then the crucial characteristic of the rheumatic candidate may be a delay in his immune response to hemolytic streptococci. As stated, following a hemolytic streptococcal infection a nonrheumatic person either (rarely) develops no rise in antistreptolysins, or generally develops a prompt response with a maximal antistreptolysin titer within 20 days. If the rheumatic subject makes either of these two responses he escapes an attack. That is, if there is no antistreptolysin response there is no attack, or if the increased antistreptolysins appear promptly and reach their maximum early and normally (within 20 days) there is no attack. But if, as frequently happens, the rheumatic patient develops an intense delayed antistreptolysin response a week or more after the normal response should have occurred, acute rheumatism develops.

In conclusion, Coburn stated that until now there has been no evidence whether the antistreptolysin curves seen in rheumatic fever were normal responses to hemolytic streptococcus infection or not. His data would indicate that the immune responses of the rheumatic patient differ from the normal chiefly in that they are delayed. This being so it may be assumed that the rheumatic subject who develops an attack handles the products of hemolytic streptococci peculiarly, involving a delay in the final elimination of hemolytic streptococcal products from the body. Why such a delay occurs or how it is associated with the development of the disease is undetermined.

*Factor of Bacterial Allergy.* Poynton's simple interpretation of what is presumably meant by bacterial allergy seems worthy of inclusion:

Assume that an infected focus is a streptococcal depot more or less constantly pouring into the circulation the body-protein of streptococci, which acts as a foreign body circulating in the human system. Such foreign substances stimulate the production of specific antibodies, hence are called "antigens." Antigens arising in a focus of infection and circulating in the body will stimulate certain tissue cells to produce antibody and in doing so this will sensitize these cells. If the response to antibody is prompt and abundant a surplus of this antibody will appear in the circulation and from now on antigen escaping from the focus of infection will meet this surplus antibody in the blood stream and be neutralized there, consequently will not reach the tissue cells. But should the production of antibody be deficient and there be no surplus in the blood stream, but the whole amount be kept back in the producing cells, a different situation arises. The continuous supply of antigen from the focus of infection has then no antibody meeting it in the blood stream, and hence will not be neutralized there but will once more reach the cells which, however, now contain a store of antibody. The antigen then combines with the antibody in the cells and this clash of antigen and antibody will irritate those cells. Thus this antigen, which was formerly innocuous to the cells when they contained no antibody, now acts as a cellular poison to them because they contain antibody. Such reactions are called hypersensitiveness or allergy. Under the theory of bacteremia or bacterial toxemia as the cause of rheumatism (which Poynton espouses) it is supposed that streptococci by their presence or by their toxins produce the local articular (and other) lesions by local infections, but the theory of bacterial allergy assumes that the antigens (streptococcal products) are not toxic per se unless or until they clash with antibody in the tissue cells.

Swift's concept of rheumatic fever as a manifestation of bacterial allergy

is well known, has been discussed herein before<sup>245, 246, 247</sup> and needs no detailed repetition. He considered it obvious that rheumatic fever patients are unusually hypersensitive to many different injurious agents, but mostly to streptococci. Although all the possible relationships between hyperergy and rheumatism have not been explored the concept clarifies much that seems inexplicable otherwise. However, Schlesinger found it difficult to explain valvular vegetations and pericardial "bread and butter" exudate purely on an allergic basis. He regarded those who believe allergy to be the fundamental cause of rheumatism "still somewhat hazy in their reasoning." "A much stronger case will have to be made out for allergy before such striking, marked changes are regarded as anything but the inflammatory result of an infective agent at the site."

*Virus Theory.* The isolation of "virus bodies" from exudates of rheumatic patients was recently reported but the disease had not been experimentally reproduced.<sup>247</sup> Swift raised two objections to the theory: 1. Filtrable viruses apparently do not produce fibrinoid degeneration, a basic pathologic feature of the disease. 2. No virus for rheumatic fever has been definitely discovered. The results of Swift's 15 years' search for such a virus were essentially negative; methods by which he sought them were briefly summarized. Either virus was not present in material used or the various animal species tested were not susceptible. Nevertheless a possible symbiotic relationship between virus and bacteria must be borne in mind. Possibly an allergic state makes the tissues susceptible to a hypothetical specific virus, or vice versa, possibly such a virus may cause an allergic state so that bacterial infection or other traumatic insult sets off an acute attack.

*Synergism of Infection and Vitamin C Deficiency.* Rinehart restated his concept that the disease may be due to the combined influence of vitamin C deficiency and infection (as discussed previously in Reviews 2 and 3). It is based on the experimental production of subcutaneous nodules, cardiac and articular lesions, "comparable to those of rheumatic fever" (and to a certain extent of atrophic arthritis), in guinea-pigs subjected to the influence of both infection and vitamin deficiency, but not in those subjected to either factor alone. He further noted a borderline or frank vitamin C deficiency in the diets of most rheumatic children. Plasma ascorbic acid levels usually parallel the vitamin C intake.<sup>213</sup> Rinehart, Greenberg and Christie noted a lowering of plasma ascorbic acid in almost all of 21 patients with acute rheumatic fever, in many with the disease quiescent. It has not been determined whether the reduction was due to inadequate intake, or to the anorexia, digestive disorders or depletion by the disease itself.

Various cardiac and articular lesions were produced by Schultz in guinea-pigs subjected to infection and experimental scurvy, alone and in combination. Infected scorbutic animals developed focal interstitial valvulitis, fibrinoid degeneration, occasionally focal, nonpurulent myocarditis. Non-infected scorbutic animals developed lesions similar but of less extent. In

either case Schultz regarded them as only slightly resembling those of rheumatic fever. No verrucous endocarditis was seen and the myocardial lesions were few and did not closely resemble Aschoff bodies. Scorbutic changes were noted in and around joints but were not enhanced in the infected animals. In 8 of 13 patients with rheumatic fever, some degree of ascorbic acid deficiency was noted by Sendroy and Schultz. It was ascribed to poor diets in two instances, to vomiting or incomplete absorption in six cases. They concluded that ascorbic acid deficiency is not specific for rheumatic fever, is probably incidental in this disease, and did not seem to be a predisposing factor.

*Conclusions on Etiology.* Although interested in the conjecture that the disease represents a symbiosis between virus and streptococci, Schlesinger did not regard any current theory with satisfaction. The so-called specific streptococci of Poynton and Paine, Birkhaug and Small do not produce lesions characteristic of the human disease and are found in the throats of nonrheumatic persons. Hemolytic streptococci are not present in the throats of normal persons; but some patients severely infected therewith do not get rheumatic fever and the disease is obviously not precipitated by a specific strain. Reviewing his own work and that which has followed it, Poynton concluded that the cause of the disease is a diplostreptococcus of a special type (which on various media appears as a streptococcus, or even a staphylococcus), a constitution of a special type, a focus of infection, an invasion of the system by streptococci and the formation of foci of a peculiar type within the body in "the connective tissue skeleton" and the development of poisons injuring the "noble tissues," heart, brain and so forth. "The future must decide whether [streptococci] are gangsters, or the accessories of gangsters, or just the watching crowd always in the way and never doing anything themselves, a rôle not peculiar to streptococci."

#### TREATMENT OF RHEUMATIC FEVER

Treatment remains essentially as before: Its general principles were reviewed by many.<sup>527, 532</sup>

*Bed Rest.* This should be continued after all symptoms have disappeared, for at least two weeks in those without evidence of carditis; for months (6 or more), not weeks, in those who develop carditis.<sup>461, 577</sup> It should be continued until the patient has gone six to eight weeks with no signs or symptoms of disease and with a normal sleeping pulse rate (well below 90 per minute).<sup>22</sup> Adequate rest involves the use of appropriate sedatives.

*Salicylates.* Salicylates are still considered "extremely useful."<sup>22, 461</sup> Some believe they shorten the disease and minimize danger to the heart.<sup>353</sup> Others believe they do not affect the proliferative reactions, for which drugs are of little value. But the action of salicylates on the exudative features of the disease is almost specific and diagnostic, affecting other types of fever

or effusion in no comparable manner.<sup>138</sup> One must not conclude that the disease is necessarily inactive when fever is controlled by salicylates; Poynton disapproved "desperate efforts" to lower temperatures thereby. Some used large,<sup>353</sup> others used smaller doses.<sup>56</sup> Kaiser concluded that acetylsalicylic acid, combined with magnesium oxide, was superior to salicylates alone in controlling joint pains and chorea and, in preventing recurrences, but not in relieving carditis.

*Other Drugs.* Poynton preferred tolysin to salicylates. Pyramidon was used by some,<sup>56</sup> avoided by others for fear of granulocytopenia.<sup>7</sup> Some considered digitalis valuable in congestive failure, useless in controlling tachycardia.<sup>22</sup> Although it occasionally slows the pulse and improves circulation its results are disappointing unless fibrillation is present.<sup>138</sup>

*Removal of Tonsils and Other Foci.* Kaiser summarized the effect of tonsillectomy on 48,000 rheumatic children. Tonsillectomized children are less likely to develop subsequent rheumatic fever and carditis, but as likely to develop muscular rheumatism and chorea as those who retain their tonsils. However, the incidence of recurrent attacks of rheumatic fever is not influenced by tonsillectomy done either before or after an initial attack. Tonsillectomy does influence end-results of the disease. The mortality was nearly twice as high among children in possession of their tonsils at the initial attack as among those tonsillectomized before their initial attack. "Tonsillectomy is justified in practically every rheumatic child until other factors that influence this disease are better understood."

When performed, tonsillectomy should be done after the acute phase of the disease,<sup>455</sup> and only when there is evidence of diseased tonsils.<sup>135</sup> Even then it should be considered a major operation with preoperative and postoperative bed rest.<sup>353, 521</sup> The danger of exacerbations after tonsillectomy can be "greatly lessened" by the daily administration of acetylsalicylic acid for one month after tonsillectomy.<sup>7</sup> Wallace and Smith found no evidence that the very early removal of tonsils of children (before the age of five years) protected them against rheumatic fever.

*Vaccines.* The use of streptococcal vaccines was "unsound," according to some,<sup>7</sup> useless according to others. Stroud gave vaccine intravenously to children for three years: those vaccinated did no better than the unvaccinated.

*Serum.* Hoping that the blood of patients recovered from rheumatic fever might contain enough antibodies to help those with active disease, Archer treated four patients intrathecally with small doses of convalescents' serum. Results were "suggestive enough" to warrant further clinical trial.

*Transfusions.* Weiss noted "satisfactory results" from the use of multiple small (150 to 250 c.c.) citrate transfusions. Results in one case were reported; others were to be reported later.

*Vitamin C.* Many of the rheumatic children studied by Rinehart were on a diet low or frankly deficient in vitamin C. Preliminary results from



diets rich in vitamin C were "encouraging." Many patients gained weight; a number suffered respiratory infections without rheumatic exacerbations. However, the oral administration by Schultz of 100 mg. of ascorbic acid (redoxon) daily for several months to 28 rheumatic patients did not lower the incidence of subsequent rheumatic activity as compared to a control group treated by lactose. Another group of 17 patients with active rheumatic fever were given 250 mg. of ascorbic acid daily by mouth or intravenously for from one to five (average 2.5) months; some were also given 200 c.c. orange juice daily. The disease was not affected thereby. Wright also was unable to affect the course of the disease by giving cevitic acid (ascorbic acid, crystalline vitamin C) in doses as large as 1000 to 2000 mg. intravenously daily. Rhinehart does not believe that lack of response to vitamin C therapy necessarily disproves the etiologic importance of vitamin C deficiency; the latter may be only one factor in preparing the soil for infection. But Wright believed that the disease, if related to a deficiency, should be ameliorated to some degree by such large doses.

*Fever Therapy.* The chorea of 16 children with active carditis was being treated with foreign-protein fever by Sutton and Dodge. Nine of the children lost signs of activity during the course of treatment, in the rest the carditis was clinically inactive within seven to ten days thereafter. Subsequently, seven patients with subacute carditis without chorea were treated with artificial fever (two to five hours, at 105° to 106° F. for one or two sessions); soon thereafter signs of active carditis disappeared or notably diminished. Further investigation seemed warranted.

*Additional Therapy for the Heart.* Severe angina pectoris may occur in young people with rheumatic carditis. Attacks may appear at night; recumbency seems to precipitate them. Good results (better than in arteriosclerotic angina) were obtained by Bland and White in four such cases by paravertebral injections of procaine and 95 per cent alcohol, blocking sympathetic rami of the first four dorsal roots. Left-sided injections were usually effective, bilateral injections were occasionally made.

*Institutional Care; Climate.* Active subclinical carditis may long persist, sometimes even with a normal sedimentation rate (Sutton). Therefore prolonged observation and care are required before and after patients are returned to their homes, to activity and to school life. Rheumatologists and cardiologists are heartily approving convalescent and rest homes, sanatoria for the prolonged supervision of convalescence, and schools for "cardiac cripples" as an important intermediary between hospital care and an active routine which, begun too early, may provoke exacerbations.<sup>439, 455, 465</sup> By such "rheumatism schemes" as that in Cardiff<sup>498</sup> or that of the London County Council coöperating with voluntary hospitals and rest homes, much has been done to "commute the sentence of death" from rheumatic fever. The established institutions and "cardiac schools," however, cannot deal with more than a fraction of the cases, and it is impossible to send most patients for a prolonged stay in the tropics.<sup>138, 532</sup>

*Prophylaxis.* The multiplication of convalescent homes, special clinics, and rheumatism supervisory centers may prevent more deaths, but not the disease. McSweeney called it "philanthropy not prophylaxis." Current methods for prophylaxis are inadequate as the incidence of the disease shows. There is therefore great need for the institution of an active, sustained crusade against the disease, following general principles similar to those so successfully employed against tuberculosis. This involves better personal and social hygiene, more effective child welfare schemes and school medical service under which physicians and nurses exercise closer supervision over children's health. Rheumatic fever should be a notifiable disease; notification would permit subsequent sociologic and epidemiologic studies of the greatest importance (Ritchie).

#### SYDENHAM'S CHOREA

Chorea accompanied rheumatic fever in 5 to 34 per cent of recent cases; it was an initial symptom in many (21 to 28 per cent).<sup>11, 85, 197, 572</sup> It was rare in India.<sup>80</sup> Statistics indicated that chorea per se is a mild manifestation of rheumatism but may be associated with severe, even fatal, carditis.<sup>11, 197</sup>

Most writers agreed that chorea is most commonly caused by rheumatic fever but can be precipitated by other factors: fright, chilling, emotional shock, fatigue. Smith and Markey stressed the emotional factor; Guttmann noted its incidence with psychoses. Poynton regarded rheumatism the main, fright a rare, cause; fewer London children had chorea the year of the terrifying war-bombings than the following year.

In acute chorea Payne and Schlesinger noted either no rise of the sedimentation rate (in 44 per cent of cases) or only a slight transient rise (in 56 per cent). It was no index of choreic severity or of impending carditis. Indeed rates were often very low. Struthers and Bacal noted normal sedimentation rates and Schilling counts.

*Treatment.* Large doses of phenobarbital controlled a case of severe chorea of 4.5 months' duration in a child, aged 11, seen by Litchfield, Gillman, Harris and Cohen. During four weeks' treatment the dose was gradually raised from 1.5 to 22 grains daily without toxicity. Smith considered nirvanol therapy drastic, sometimes dangerous because of its effect on bone marrow.

Several reports testified to the superiority of fever therapy over other methods. Of 50 patients treated by Weisman and Leslie with fever reactions from typhoid vaccine 46 became symptom free, two improved, two did not; only five patients had recurrences within three years. Treatments were given daily for seven to eight days, omitted two to four days, then continued as necessary. Generally eight or nine fever reactions (to 104° or 105°, occasionally 106° or 107° F.) were given; the greater the fever, the better the results. Those with active carditis seemed to do as well if not

better than others. Results of similar treatments were excellent in six, poor in two, of eight cases seen by Litchfield and his colleagues. Fever reactions to 104° or 105° F. were induced daily for 7 to 12 days.

The results of Sutton and Dodge were even more striking. Among 150 patients treated by orthodox methods the average duration of chorea after therapy was begun was 43 (10 to 180) days. Of 150 patients treated with triple typhoid vaccine symptoms averaged only 9 (2 to 47) days after treatment. Vaccine injections were given daily, with an occasional rest day, until chorea stopped. The number of injections averaged five in mild cases, six in moderate cases, nine in severe cases (maximum 18). Because typhoid vaccine fever reactions are not as controllable as artificial fever, 16 other patients were treated with the latter (radiant energy). Results from only one or two artificial fever sessions were as good as those from several vaccine-fevers. Subacute carditis was not a contraindication, indeed it seemed to be relieved.

Excellent results from artificial fever were noted by others. All of 13 patients treated by Barnacle, Ewalt and Ebaugh were "cured." No recurrences were noted within one year. Six cases of "most severe" chorea of two weeks to 10 months' duration were slowly but completely stopped by similar treatments given by Metz. Symptoms disappeared within two to four weeks. Neymann, Blatt and Osborne also noted excellent results from fever (electro-magnetic induction) in 25 cases; nine very severe, six moderate, ten mild. From two to ten (av. four) treatments were given, two per week. Recurrences occurred in 12 per cent. Complications were a heat convulsion in one case, transient albuminuria and hematuria in one case.

#### CHRONIC ARTHRITIS

*General Remarks on the Relationships and Distinctions between the Two Great Types.* Those who espouse the "unitarian idea" consider atrophic and hypertrophic arthritis varieties of one disease, differences being due chiefly to the factor of age, physiologic rather than calendar. To them atrophic arthritis represents the reaction of physiologically young tissues against an insult; hypertrophic arthritis is the reaction of physiologically aging tissues against the same insult. Others, more equivocal, believe the two great types are very closely related etiologically, but are probably different diseases. Some believe that both types of chronic arthritis are often the result of similar factors.<sup>279, 380</sup> Most rheumatologists, however, stress the distinctions between the two types and consider them totally unrelated diseases, "sharing little but a common battleground."<sup>165, 223, 383</sup> Citing the manifold constitutional, clinical, cytologic, chemical, immunologic, pathologic, roentgenographic and prognostic differences between them they would conclude with Boots: "There would now seem to be no further excuse to look upon these cases as examples of a single disease." The frequency of patients with mixed (clinical, not just radiologic) types, who demonstrate

both atrophic and hypertrophic arthritis in different or even in the same joint, does not confuse those who realize that every young or middle-aged patient with atrophic arthritis will, if he lives long enough, develop hypertrophic arthritis, since the latter is a histologic (although not necessarily a symptom-producing) inevitability to all persons over 50 or 60 years of age. Then too, patients over 50 years of age with hypertrophic arthritis are not immune to atrophic arthritis which even the elderly may develop independently of their coincidental hypertrophic arthritis.

*Clinical and Pathologic Distinctions.* The familiar clinical and pathologic distinctions between atrophic and hypertrophic arthritis were again reviewed.<sup>48, 194, 195, 290, 300</sup>

*Cytologic, Chemical and Immunologic Differences.* These were again summarized<sup>83, 180, 243</sup> (table 1).

*Roentgenographic Differentiation.* According to S. G. Scott clinical diagnoses of the chronic arthritides can be made with considerable accuracy from roentgenograms alone, particularly of hands. Others<sup>4, 172, 177, 504, 535</sup> regard roentgenographic differences as highly suggestive but not pathognomonic. They believe that a final clinical diagnosis cannot be based on roentgenograms alone; features of the latter must be correlated with clinical and biochemical findings. Although osteophytes are much commoner in hypertrophic arthritis, they are frequently seen in late atrophic arthritis, especially in weight bearing joints, or they may occur in almost any infectious type of suppurative or nonsuppurative arthritis. A radiologist, noting these osteophytes and having no knowledge of the clinical features, will often classify such a case as hypertrophic arthritis (a diagnosis correct in the radiologic sense but incorrect in a clinical sense).<sup>177</sup>

The comparative radiology of the two great types was noted by several.<sup>5, 172, 504, 535</sup> Taylor and his colleagues noted the following: marked systemic decalcification in 95 per cent of cases of atrophic, but only mild decalcification consistent with age in 75 per cent of cases of hypertrophic arthritis; also local decalcification in 13 per cent and 6 per cent, respectively; bone production (lippling and osteophytes) in 77 per cent and 100 per cent; "atrophic bone destruction" (punched-out areas) in 85 per cent and 9 per cent; "active bone destruction" in 11 per cent and 0 per cent; cartilage destruction (narrowing of joint space) in 95 per cent and 59 per cent; fusiform enlargement of soft tissue in 88 per cent and 9 per cent. Ankylosis occurred in 26 per cent of the atrophic, in only 6 per cent of the hypertrophic, cases; in the latter only in the spine. Although individual features were shared by both types of arthritis, each possessed a basic pattern or grouping of features which makes roentgenograms very helpful in differentiation. The two types are radiographically distinct, even when they coexist in the same joint.

An appraisal of the diagnostic worth of the finer radiologic differences was made by Spackman who studied 1000 cases of chronic arthritis in patients aged 9 to 76 years: 474 with atrophic, 526 with hypertrophic arthritis.

Asymptomatic cases of the latter were not included. Changes in atrophic arthritis were as follows: in the early stage there were rarefaction of the trabeculated ends of bones, preservation of the zone of provisional calcification but irregularities therein, homogeneous haziness at joint space, at first widening, later narrowing of joint space. The earliest recognizable change was roughening or slight irregularity of the zone of provisional calcification, very minute projections of new bone into cartilage and small irregular areas of decreased density especially in the proximal border of the zone. In intermediate and late stages there was progressive ground glass atrophy, soft tissue swelling, disappearance of the line of provisional calcification and bony ankylosis of the joint. Changes in hypertrophic arthritis were as follows: in the early stage there were small, marginal osteophytes, narrowing of joint space, change in alignment of bones, thickening of the provisional zone of calcification, irregularity of the bony articulating surfaces, broadening of the circumference and secondary atrophy of the honey-comb type; in the intermediate and late stages, spur formation, Heberden's nodes, eburnation of bone, displacement and subluxation, punched-out areas, gross deformity and advanced secondary atrophy.

Morrison and Kuhns studied 55 cases of atrophic, 11 of hypertrophic and 7 of "mixed arthritis" to note the changes in serial roentgenograms taken from four to ten years or more apart. The changes varied greatly in different patients and in the same patient at different ages, and at different stages of the disease. The changes in atrophic and hypertrophic arthritis were not pathognomonic, and differed from those in the more acute and specific arthritides chiefly in the slow rate at which the former progressed. Marked changes were compatible with good function. Even though the radiologic changes were increasing, good functional recovery was possible. Changes in roentgenograms usually progressed long after the disease was clinically quiescent. Improvement in the roentgenologic picture was rarely seen; recalcification of bone and moderate repair were observed in the roentgenograms of only two patients. On a radiologic basis, Scott subdivided atrophic arthritis into "rheumatoid arthritis" and "infective arthritis," general decalcification being the keynote of rheumatoid arthritis, loss of cartilage with early bone sclerosis at the affected joints being the feature of infective arthritis. Others<sup>4, 535</sup> found no radiologic basis for such a subdivision of atrophic (rheumatoid) arthritis. Aldred-Brown and Stevens did notice two "varieties," some with dominant local changes, others with dominant systemic bone changes. But they often occurred together and there was no evidence that the one type was associated with infection; the other, not.

*Constitutional Differences; Anthropometric, Psychologic.* Some affirm, others deny that atrophic arthritis occurs chiefly in the asthenic, and osteoarthritis in the pyknic, type. Anthropometric studies by Kovacs, Hartung and Hanscom on 50 patients with atrophic and 50 with hypertrophic arthritis revealed marked differences in constitutional morphology. Those with at-



rophic arthritis had a tendency to increased longitudinal measurements, longer and thinner necks, slender but not necessarily tall build, with weights normal or subnormal. Those with hypertrophic arthritis had a tendency to obesity, increased horizontal measurements, short thick necks, massive silhouettes.

(These 100 patients were all females; it would be interesting for the same investigators to make identical studies on males.—Ed.)

Psychologic differences between patients with atrophic arthritis and those with hypertrophic arthritis were noted by Eelman and Mitchell, but not by Kovacs, Hartung and Hanscom.

#### ATROPHIC ARTHRITIS

*Incidence.* Factors influencing the incidence of this disease are similar to those which influence rheumatic fever. Atrophic arthritis rarely appears among native whites or Indians in the Arizona desert.<sup>269</sup> Winter produces its harmful effects by cold and damp, not by cold alone.<sup>69</sup> The patient's resistance is lowered by overheated houses and excess clothing, by the greater incidence of colds and tonsillitis which may provoke the disease and by a lack of adequate exercise and sweating. The peak incidence in the cases of Dawson and Tyson was between February and April. The disease is rare in children; only 10 of 800 patients seen by Dawson and Tyson were under 12 years of age. Among Pemberton's 300 patients of all ages 3 per cent were children. To Irons the influence of heredity seemed obvious: the disease often appeared in grandmother, mother and daughter. In Dawson and Tyson's series the familial incidence was 15 per cent.

*Symptoms and Course.* Some English writers spoke of two varieties: 1. "Primary rheumatoid arthritis" or "rheumatoid arthritis" is of insidious afebrile onset and is accompanied by no marked inflammation and no obvious or related foci. 2. "Secondary rheumatoid arthritis," "chronic infective arthritis," or "focal arthritis" usually is of acute or subacute febrile onset and is accompanied by considerable inflammation and obvious foci to which it is supposedly secondary and after removal of which notable improvement is expected. Because the basis for complete separation of these two varieties is not clear, the American Rheumatism Association has not recognized such a subdivision of atrophic (rheumatoid) arthritis.

*Complications.* Cardiovascular disease occurs only with the expected frequency in patients with atrophic (but with increased frequency in those with hypertrophic) arthritis, according to Monroe and Walcott. In 142 patients with atrophic arthritis cardiac enlargement occurred in 6 per cent, hypertension in 10 per cent, arteriosclerosis in 11 per cent, varicose veins in 5 per cent. Cardiovascular decompensation was rare; angina pectoris did not occur in this series.

Rheumatic iridocyclitis occurs not infrequently in children with chronic

polyarthritis; it often has a chronic course, causing ribbon-like keratitis. Holm reported a case in a 15 year old girl with Still's disease (adenopathy but no enlargement of liver or spleen). The probable rheumatic nature of primary juvenile iridocyclitis should be kept in mind. In such cases the iridocyclitis may come before, with, or after the arthritis.

*Atrophic Arthritis and Splenomegaly; Still's Disease; "Felty's Syndrome."* The association of arthritis with splenomegaly, sometimes with adenopathy, hepatomegaly, anemia and leukopenia or leukocytosis was described by Chauffard and Ramond (1896), Still (1897) Herringham (1909) and others; more recently by Felty (1924). The third review contained comments on the relationship between these syndromes, particularly on whether Felty's syndrome was different from or identical with Still's disease. Williams reported a case of Felty's syndrome with necropsy findings; he considered it not identical with Still's disease, but a blood dyscrasia in which there is an arrest in the maturation of polymorphonuclear leukocytes. Singer and Levy, who also reported two cases with necropsy findings, concluded that Felty's syndrome and Still's disease were slightly different varieties of the same disease, both being manifestations of sepsis lenta usually from green-producing streptococci. Features of the Still-Chauffard syndrome as described in European literature were summarized by Singer and Levy. Williams noted the characteristics of the nine cases of "Felty's syndrome" so far reported. The disease appeared in persons aged 45 to 65 years, of either sex. Features were weight loss (average 40 pounds), intermittent moderate fever ( $99^{\circ}$  to  $101^{\circ}$  F.), chronic polyarthritis with repeated acute migratory exacerbations, roentgenograms showing "infectious arthritis" or mild indeterminate changes, splenomegaly (all nine cases), hepatomegaly (two of nine cases), pigmentation of skin (six of nine cases), slight general lymphadenopathy (five cases), leukopenia (800 to 4200 cells, av. 2500); 14 per cent to 79 per cent (av. 50 per cent) polymorphonuclears, 1 to 12 per cent eosinophiles, 14 per cent to 86 per cent (av. 40 per cent) lymphocytes, occasional myelocytes. (All of these features are often seen in cases of atrophic arthritis.—Ed.) In William's own case cultures of blood in life and of liver and spleen at death were negative; the patient died of pneumonia, lung cultures revealed green-producing streptococci. Blood cultures in the cases of Singer and Levy revealed green-producing streptococci before death.

(Further observations will be necessary before one can form a final opinion on the relationship between Still's disease and Felty's syndrome. From data at hand we believe they are both varieties of atrophic arthritis. That Felty's syndrome is a sepsis lenta does not appear to be proved. Many chronic wasting illnesses terminate with a bacteremia of one sort or another.—Ed.)

*Relation of Atrophic Arthritis to Other Diseases.* Possible relationships between atrophic arthritis and rheumatic fever, and tuberculosis and atrophic arthritis, were discussed under "rheumatic fever" and "tuberculous rheumatism."

*Pathology.* With Deacon, Ghormley again stated that the focal collections of lymphocytes in synovia and adjacent bone marrow are the distinctive pathologic features of the disease. Present early and late, they bear no relationship to the duration of the disease. Contrary to the opinion of Fisher (1929) and of Jordon, the collections are not perivascular, as can be seen when tissues are stained with the Perdreau stain. Miller<sup>368</sup> regarded the focal collections as "evidence that rheumatoid arthritis is an inflammatory disease of probable bacterial origin."

*Roentgenographic Features.* These were discussed.

*Laboratory Data; Blood Counts.* A left-shift in the Schilling hemogram was noted by Cecil in 68 per cent of 28 cases, by Collins in 97 per cent of 59 cases. Unaffected by removal of foci, it was found even in cases of long duration. "The persistence of the shift lends support to the view that this disease is truly infective in nature and that the infection is not a transient phenomenon during the inception of the disease, which is often pyrexial, but continues as an infection capable of exerting its influence on the nuclear count for many years." Hartung, Davis, Steinbrocker and Straub found the nonfilament count elevated above 16 per cent (av. count 30 per cent), in 96 of 100 cases of atrophic arthritis. Of 100 cases of hypertrophic arthritis the count was elevated in 53 (av. count 22 per cent), normal in 47. "The high incidence of an elevated nonfilament count in atrophic arthritis suggests the presence of an infectious agent." A normal count indicates that atrophic arthritis is very likely not present.

*Sedimentation Rates and Blood Proteins.* Davis noted the following sedimentation rates: 43 to 125 mm. (1 hour) in eight severe cases, 15 to 80 mm. in eleven moderately severe cases, 28 to 62 mm. in five clinically arrested cases. The rate demonstrates roughly whether there has been a change in globulin or fibrinogen or both, provided correction is made for cell volume. Theoretically a diminished rate is not always an accurate index of improvement from vaccines, certain of which cause a rise in globulin which per se may increase the rate. Such was not the case with Davis' use of hemolytic streptococcus vaccine. In atrophic arthritis there was a rise in globulin, especially euglobulin, and in fibrinogen; a fall in albumin. These findings suggested to Davis that atrophic arthritis is an infectious disease.

The plasma cholesterol tends to be low in atrophic arthritis (high in hypertrophic arthritis). Serum calcium was normal.<sup>130, 243</sup>

*Gastric Analysis.* Deficient gastric acid was present in 60 per cent of Collins' female and in 17 per cent of his male patients. It bore no relationship to the degree of left shift in nuclear counts. Fletcher noted gastric subacidity in 50 per cent of patients studied; many were anacid to alcohol, a few even to histamine. He estimated that anacidity is five times as frequent among arthritic patients as among normals. Histamine-refractory achlorhydria was found by Moltke and Ohlsen in 36 per cent of 30 cases of

atrophic arthritis. The high incidence of achlorhydria was not accounted for by age or sex incidence. "It possibly predisposes to the disease and may be a factor of much significance. Perhaps it is an expression of an infective process of gastric mucosa which is responsible for the poor nutrition of the arthritic."

(How can achlorhydria be of primary significance when it is so inconsistently present? Gastritis has not been noted at necropsy in atrophic arthritis.—Ed.)

*Synovial Fluid.* The cytology of 52 synovial fluids from 31 patients was noted by Collins to be as follows: total nucleated cells, 5060 to 56,000 (av. 20,170) per cu. mm.; differential count (in per cent) polymorphonuclears 41 to 95 (av. 80); lymphocytes 3 to 45 (av. 16); monocytes 1 to 14 (av. 3); macrophages 0 to 3 (av. 0.3); synovial cells 0 to 3 (av. 0.4). The total protein per cent was 2.7 to 8.5. The polymorphonuclear count depends on three factors: depth of the inflammatory process within synovial tissues, extent of synovia involved, type of inflammation present—acute, subacute or chronic.

#### ETIOLOGY AND PATHOGENESIS OF ATROPHIC ARTHRITIS

*Factor of Infection: 1. Foci of Infection.* On the basis of the literature under review the pendulum could hardly swing farther away from the subject of foci of infection and keep it alive. While many writers commented academically on the subject, less than a half dozen reported new investigations thereon. Cultures of foci made in the usual way reveal more germs than those made by the pathogen-selective method (Solis-Cohen, 1927) but most of the bacteria thus isolated are of no significance, according to Murphy. In the pathogen-selective method the patient's whole fresh blood may inhibit the growth of nonpathogenic bacteria, thus allowing the "specific" organism to grow out in pure culture. Among 107 patients with "chronic arthritis" Murphy's results, by the usual and the special method respectively, were as follows: positive cultures from nose in 100 per cent and 47 per cent, from throat in 100 per cent and 79 per cent, from feces in 100 per cent and 24 per cent, from urine in 61 per cent and 34 per cent. Bacteria recovered by both methods were streptococci and staphylococci, the former more often from throats and feces, the latter from nose and urine.

(Because of insufficient data no significance can be attached to these figures. Although the four cases reported seem to have been of atrophic arthritis, no evidence was given as to the type of "chronic arthritis" present in the other cases. No animal injections were made to support the contention that the bacteria isolated by the pathogen-selective method were more significant. Their significance was assumed on the basis of results from vaccines.—Ed.)

An infected prostate is an important, often a more dangerous, focus than others because it so often escapes detection, according to Duncan. Of

752 males with "chronic arthritis" who had prostatic examinations 41 per cent had definite prostatitis, 40 per cent had a history of gonorrhea. Prostatic foci were commoner than oral foci as the latter had often been removed.

(No bacteriologic work was reported. A clinical relationship was assumed on the basis of improvement in joints during prostatic therapy.—Ed.)

Foci of infection of "etiologic importance" were present in 72 per cent of the cases of Davidson and Goldie, oftener in tonsils, throat and sinuses than in teeth. Asymptomatic colon bacilluria, noted in 8 of 24 cases, was considered of etiologic significance by Slot and Deville. In spite of such data, Joseph Miller concluded that there was no convincing clinical or experimental evidence that chronic foci of infection are responsible for atrophic arthritis. According to Fisher, the National Committee on Chronic Rheumatic Diseases of the Royal College of Physicians were of the opinion that the etiologic import of toxic foci is often exaggerated; although in some cases foci appear to be important, on the whole their significance has not yet been definitely established.

2. *Blood Cultures.* Positive blood cultures were obtained by McEwen, Alexander and Bunim in 19 (54 per cent) of 35 cases: hemolytic streptococci in three, green streptococci in nine, indifferent streptococci in five, diphtheroids in three cases. Cultures were positive (for green-producing streptococci) in 5 per cent of 44 normal controls, in 25 per cent of senescent nonfebrile states. Therefore the streptococci recovered from the arthritic patients were considered unrelated to the disease. Without discussing their significance, Cecil stated that the bacteria isolated by him and by others were actually in the blood and not contaminants. Cultures of blood and joints made by Davidson and Goldie were "consistently negative" (no figures given).

3. *Cultures of Joints.* The studies of Hadjopoulos and Burbank led them to propose the following hypothesis: If the cause of atrophic arthritis were a specific, immutable microorganism with stable immunogenic properties, the disease should resemble other acute infections and end by recovery if the system uses its defensive forces effectively, or by death if it is overwhelmed by extremely virulent invaders. But if the disease were due to a streptococcus capable of dissociating into microbic forms more resistant to the immune mechanism, the natural tendency of the host would be to encourage such a metamorphosis. At operation cultures were made from joints in 20 cases of atrophic arthritis: they were sterile in two inactive cases of arthritis, revealed diphtheroids in two slightly active cases, *Staphylococcus albus* or *aureus* and diphtheroids in eleven moderately active cases, streptococci in three active cases (green-producing in two; hemolytic in one). One patient with subacute tenosynovitis yielded *Micrococcus tetragenus* and sarcina; one with acute bacteremic arthritis yielded *Streptococcus hemolyticus*. One culture of hemolytic streptococci during a period of three months passed



through all these stages. It was concluded therefore that atrophic arthritis is caused by a multiple mutant infection—at first by a streptococcus which gradually changes into a diphtheroid, staphylococcus, or "*Micrococcus sarcina*." This may explain why sera of arthritic patients frequently react to a variety of apparently unrelated organisms.

(This interesting work needs considerable repetition for its final acceptance.—Ed.)

4. *Agglutinins.* It was reported again that most patients with atrophic arthritis possess agglutinins to hemolytic streptococci, generally in high titer; a few also possess agglutinins to green-producing streptococci usually in rather low titer (table 1). Agglutinins were not strain specific and tended to diminish, eventually disappear, as recovery took place. Of 36 patients with active atrophic arthritis McEwen and colleagues noted agglutinins to hemolytic streptococci in 85 per cent; in a dilution of 1:20 in 6 per cent; 1:40 in 3 per cent; 1:80 in 20 per cent; 1:160 in 8 per cent; 1:320 in 6 per cent; 1:640 in 42 per cent. No agglutinins were present in three cases of inactive atrophic arthritis or in 35 normal controls. Hartung and his colleagues noted agglutinins to hemolytic streptococci in "significant dilutions" (1:160 or over) in 24 to 36 per cent of cases depending on the strain used, in only 10 per cent of controls; agglutinins to various strains of green-producing streptococci in 4 to 16 per cent of cases. Fewer agglutinins were present to hemolytic streptococci from fatal septicemia than to those of less virulent nature. Davidson and Goldie noted hemolytic streptococcal agglutinins in a titer of 1:200 in 75 per cent of cases of atrophic arthritis, in 5 per cent of controls. Figures reported by Goldie and Griffiths were: agglutinins to hemolytic streptococci (titer 1:100 or over) in 89 per cent of patients with atrophic arthritis, in 71 per cent of those with nonstreptococcal diseases, in 10 per cent of controls; agglutinins to green-producing streptococci were present in dilutions 1:100 in only 5 to 7 per cent of arthritic patients and controls. In sera of 76 patients Dawson and Olmstead found agglutinins practically only to streptococci Lancefield group A, not to groups B to G.

5. *Precipitins.* Strong precipitin reactions to C substance of hemolytic streptococci were observed by Dawson and Olmstead only in those sera which gave strongly positive agglutination reactions; that is, precipitation reactions in atrophic arthritis were characteristic only for group A hemolytic streptococci. The presence of common antigenic constituents produced a small number of cross reactions with extracts of other groups. Results of Chasis and McEwen were similar except for a greater number of cross reactions; the non-group-specific fraction present in bacteria and in the crude C-extracts responsible for these cross-reactions is not the nucleoprotein or P fraction; it is apparently nonprotein in nature. McEwen, Alexander and Bunim noted strong and frequent precipitations to group A streptococci not only in patients with atrophic arthritis, but also in those with rheumatic fever, with

known hemolytic streptococcal diseases and even in 24 per cent of normal controls. The test is therefore of no value in differential diagnosis.

6. *Antistreptolysins* (*Antihemolysins*, *Anhemolysins*). Dawson and Olmstead noted increased antistreptolysins in "early" cases of atrophic arthritis (less than one year's duration), particularly in those of acute or subacute onset, but not in most "late" cases (over one year's duration). The average value in 40 early cases was 125 units (in 26 it was 125 or more), that in 151 late cases was only 51 units, that in 91 controls was 62 units, only five controls having 125 units or more. McEwen and colleagues found increased antistreptolysins (over 150 units or more) in only 9 per cent of their cases of atrophic arthritis (in 3 per cent of normal controls, in 80 per cent of rheumatic fever patients). Longcope also noted distinctly lower antistreptolysin titers in atrophic arthritis than in rheumatic fever; of 55 arthritic patients 46 per cent had over 100 units, only 18 per cent had titers above 200 units. About 25 per cent of the patients of Goldie and Griffiths had 200 units or more, about 50 per cent had 100 + units.

7. *Antifibrinolysins*. Sera of patients with atrophic arthritis contain some, but not as much, antifibrinolysin as that of patients with rheumatic fever. Of 11 arthritic patients, 36 per cent possessed "definite resistance," 18 per cent possessed "marked resistance," to fibrinolysis.<sup>389</sup> Similar resistance was noted in many normal controls. Stuart-Harris found much lower values for antifibrinolysins; none in 54 of 60 patients, partial resistance (that is, some antifibrinolytic activity) in 4, "complete resistance" (that is, marked concentration of antifibrinolysins) in only 2. Conclusions were that hemolytic streptococci were related to rheumatic fever but not to atrophic arthritis.

8. *Streptococcal Skin Reactions*. Positive skin reactions to hemolytic streptococci were obtained by Goldie and Griffiths in 76 per cent (with a concentrated solution) and in 28 per cent (with a weaker solution) of their cases of "chronic infective arthritis"; in 24 per cent and 0 per cent of controls. Positive skin reactions to green-producing streptococci were noted much less often; with a strong solution in only 11 per cent, with a weaker solution in about 9 per cent of arthritic patients and controls.

*Interpretation of Immunologic Data*. The presence of these antibodies (table 1) in patients with atrophic arthritis is strong presumptive evidence that hemolytic streptococci may play some rôle in the production of the disease. But if hemolytic streptococci are etiologically related to both rheumatic fever and atrophic arthritis it is difficult to explain the immunologic differences between them.<sup>83</sup> Some of the reactions are sufficiently distinct to be useful in differential diagnosis. Agglutination and precipitin tests tend to parallel one another as do antistreptolysin and antifibrinolysin concentrations. Agglutination and precipitin reactions are strongly positive in atrophic arthritis, weak or absent in rheumatic fever, but antistreptolysins and antifibrinolysins are usually markedly present in rheumatic fever, absent

or weakly present in atrophic arthritis. Although agglutinins and precipitins are increased in atrophic arthritis they may be nonspecific antibodies, comparable to the Wassermann and Weil-Felix reactions (Myers). Some believe that the hemolytic streptococcal infection is of a different nature in the two diseases, the same agent producing a different response in each.<sup>135</sup> At present, obvious deficiencies in these tests exist; already discrepancies have appeared in the results of various workers. Until these difficulties are corrected, no final interpretation is possible.

*Bacterial Allergy.* Although bacteria play a rôle, no one specific germ causes chronic arthritis, according to Holman; it is not the germ or germs alone, it is "largely a question of the time, the place and the germ." In spite of inconclusive skin tests with bacterial proteins, Young favored the theory of bacterial allergy. Ghormley and Deacon believe the disease to be related to bacteria even though the cellular reaction in synovia is not as one would expect from intra-articular bacteria. Perhaps the focal lymphocyte collections in synovia represent an allergic response to some bacterial or other toxin. Miller believed it impossible to explain the pathologic process on an allergic basis. Myers regarded the theory inadequately supported and unproved.

*Virus Theory.* Although this theory seemed attractive to some,<sup>223</sup> no further data in support of it were reported.

*Factor of Circulatory Disturbance.* No new data on circulatory disturbances as a cause of atrophic arthritis were presented. The primary importance of such a factor seemed unproved to Myers. Histologic examination of affected synovia reveals, not vasoconstriction but a large blood supply and many open capillaries. Atrophic arthritis is a rare complication of thromboangiitis obliterans, arteriosclerotic occlusion, Raynaud's disease or scleroderma.

*Factor of Altered Metabolism; Carbohydrate.* Forbes and his colleagues considered the effect of a high carbohydrate diet harmful. But when Bowen and Lockie gave high carbohydrate (425 to 500 gm.) high calorie (2200 to 2700) diets daily for 15 to 65 weeks to eight patients with advanced atrophic arthritis no exacerbations were produced. By this diet arthritis was made neither worse nor better, but weight gains and improvement in skin texture and general nutrition were noted. The sugar tolerance of 49 arthritic patients (23 with atrophic, 15 with hypertrophic, 11 with mixed, arthritis) was tested by Peers, using the old routine test which showed delayed removal of sugar in 83 per cent, and by the new Exter-Rose test which showed abnormal curves in 57 per cent of cases. Peers concluded that the older test was more accurate and that the abnormal sugar curves reflect a constitutional disturbance of secondary, not etiologic, import. According to Myers many studies on sugar tolerance curves have been "unconvincing," done without due regard to certain factors (patient's age, nutrition, amount of sugar actually absorbed, and so forth). Carbohydrate indigestion is not

limited to arthritic patients, and when present, usually follows rather than precedes arthritis.

*Calcium.* Wooton vaguely referred to atrophic and hypertrophic arthritis as "end results of serum-calcium vagaries." No supporting data were given.

*Sulfur Metabolism and Hepatic Dysfunction.* According to Forbes and his coworkers indoluria is usually present in "chronic arthritis" (and other conditions), generally parallels the activity of the disease and disappears when joints markedly improve. Indole may arise from foci of infection, or, when these are absent, possibly from intestinal decomposition of tryptophane, indole being either formed in abnormal amounts or allowed to pass through the liver not detoxified. Sulfur is necessary for its detoxification and conversion into indican (potassium indoxyl sulfate). Indoluria may indicate impairment of hepatic detoxification resulting from a sulfur deficiency in the liver. Reputedly the sulfur content of articular cartilage and of fingernails is low in arthritis. Forbes and his colleagues produced "typical arthritic changes" in joints of rabbits by the intra-articular injection of small amounts of indole.

(Many substances will produce them.—Ed.)

Perhaps indole, passing undetoxified through the liver with other toxic substances which gain similar entrance, is a contributing factor in chronic arthritis. On the basis of this hypothesis high sulfur-low carbohydrate diets were given 22 patients with atrophic arthritis and to eight with hypertrophic arthritis, most of whom had indoluria. Twenty of the former and five of the latter "improved markedly." Coincident with improvement, indoluria ceased. Some patients whose diets were interrupted noted return of joint pains. Since the diet was low in carbohydrate and rich in sulfur and vitamin B it was admittedly impossible to ascribe relief to the sulfur alone.

*Vitamin Deficiency.* Deficiency in vitamin B, C or D has been regarded as an associated factor in the production of chronic arthritis of either type. Fletcher has suspected a latent deficiency in vitamin B. Recently Rinehart and his coworkers attempted to establish vitamin C deficiency as an etiologic factor in both atrophic arthritis and rheumatic fever. The basis for this idea was noted previously<sup>247</sup> and was restated. According to Rinehart, vitamin C deficiency in guinea-pigs produced a painful deforming arthropathy resembling atrophic arthritis—synovial proliferation, pannus formation and periarticular fibrous thickening. Superimposed infection sometimes accelerated and accentuated these pathologic processes which included changes in bone, muscle and skin. Normal plasma values for ascorbic acid are 0.7 to 0.9 mg. per cent; levels below 0.7 mg. per cent are suboptimal, those below 0.5 mg. per cent are low (Rinehart, Greenberg, Baker). Low values (0.14 to 0.66 mg. per cent) were noted in 21 patients with atrophic arthritis on their usual diet. High values (0.90 to 1.39 mg. per cent) were noted in 12 arthritic patients given an intake rich in vitamin C. (Six pa-

tients with hypertrophic arthritis had normal or high values—0.90 to 1.34 mg. per cent.) Although low levels of plasma ascorbic acid are not peculiar to atrophic arthritis and in a given case do not indicate the existence of scurvy, these consistently low values in arthritis seem significant. The mechanism involved is unexplained.

(In this connection, and apropos of Hench's observation (1933) that notable jaundice temporarily "inactivates" atrophic arthritis and fibrositis, the observation of Sendroy and Schulz is of interest: jaundice seems to increase urinary excretion of ascorbic acid. "In cases of icterus, the abnormal titration of the urine may be caused either by the increased excretion of reducing substances other than ascorbic acid, or by a real disturbance in the ascorbic acid excretion or utilization process."—Ed.)

Because several patients with atrophic or hypertrophic arthritis improved while on concentrated vitamin D, Livingston assumed that arthritis is associated in part with a vitamin D deficiency.

*Food Allergy and Dietary Habits.* Young noted that patients with atrophic arthritis are apparently abnormally susceptible to skin allergy (urticaria and allergic dermatitis) but not to hay fever or asthma. Hay fever or asthma or both were present in 15 per cent of 200 arthritic patients, in 14 per cent of 50 controls. Skin allergy was present in 32 per cent of arthritic patients, in 12 per cent of controls. However, only 4 per cent of 50 patients with allergic dermatitis and 2 per cent of 50 patients with urticaria had arthritis. In spite of the susceptibility of arthritics to skin allergy, skin reactions to food or bacterial proteins in 20 patients were of little value. Even in cases in which a known food sensitization was present, articular symptoms were not aggravated by ingestion of foods to which patients were clinically sensitive. Fifteen arthritic patients with skin allergy from known foods were fed the irritating food repeatedly; at no time was the arthritis affected. Young's results therefore do not support the idea that arthritis is caused by dietary disturbance or food allergy.

(A case of allergic synovitis presumably due to English walnuts was reported by Lewin and Taub and will be noted later.—Ed.)

*Intestinal Toxicosis.* "Though there is not sufficient laboratory or clinical evidence to show that [atrophic] arthritis is a definite disease due to errors in metabolism, clinically I believe that the primary form is metabolic and probably due to some imbalance in endocrines" (Pringle). Thus many writers vaguely blamed the disease on abnormal metabolic processes involving intestinal dysfunction, and endocrine imbalance. Others objected to the vagueness of the terms "imbalance," "dysfunction" and "metabolic error," and asked how they operate to produce arthritis. To them gastric anacidity, colonic abnormalities and carbohydrate indigestion, inconsistently present, are not the cause of arthritis but the result of prolonged illness.<sup>383</sup> Current literature included no further data.

*Endocrine Abnormalities.* With no support whatever one writer<sup>220</sup> in-



criminated practically all the endocrine glands by name in atrophic or hypertrophic arthritis. In atrophic arthritis "usually the metabolic rate is below average and sometimes well below the limits of normal" (Fletcher). Statements such as this are not uncommon<sup>52, 531</sup> and have been challenged by those who generally find normal rates. Peers noted metabolic rates below minus 9 in 14 of 39 cases of atrophic, in 17 of 28 cases of hypertrophic, and in 7 of 12 cases of "mixed" arthritis. But he concluded that "the true arthritic is a non-myxedematous individual." Low rates were not due to lack of thyroid hormone but were brought about in some other fashion and are merely another reflection of a constitutional disease.

(Certain of these low rates may be normal for the individual.—Ed.)

*Disturbance of the Sympathetic Nervous System.* No new data on this point were reported except the observation that sympathectomy provides relief to certain arthritic patients.<sup>591</sup> But because sympathectomy does not completely arrest the disease consistently and because many arthritic patients do not have vasomotor disturbances ever or until late in the disease, Myers concluded that the vasomotor phenomena, although they aggravate symptoms, are incidental and that a disturbance of the sympathetic nervous system is not the cause of arthritis.

(Obviously the cause of the disease is unknown. The editors of these reviews have been mildly criticized for not making a stronger case for the metabolic or endocrine theories, for "playing down" papers supporting these ideas. Regardless of our individual convictions we have tried to review all papers fairly, to "take them as they come." Indeed an admitted fault, perhaps a serious one, is that in our efforts to be impartial, repertorial rather than too judicial, and to give new or contentious ideas a hearing, we have been too inclusive, not exclusive enough, and have reported much inferior work herein. Paraphrasing the automobile advertisement: when better and more papers on the metabolic and endocrine theories are available, the review will welcome them. Unfortunately in the absence of much concrete evidence in favor of these theories, papers thereon have been as a rule most speculative, hypothetical and philosophical. Although unproved, the infectious theory remains dominant by the content as well as by the volume of literature thereon. However, there seems to be a current reduction in the number of papers thereon and in the zeal of their authors. Investigations on foci and blood cultures have become momentarily less popular and interest has swung to the immunologic reactions involved. These are difficult to interpret. Indirect evidence is so much less satisfactory than direct evidence that some, confused by the uncertainty and contradictions thereof, are inclined to favor the infectious theory in spite of rather than because of, all the bacteriologic and immunologic data so far presented. The importance of beta hemolytic streptococci in the etiology of rheumatic fever and atrophic arthritis should be somewhat deflated if it is shown (as preliminary and unpublished reports seem to indicate it will be shown) that sulfanilamide, so effective in diseases of known hemolytic streptococcal origin, is of little or no value in rheumatism. If so one cannot escape the conclusion that such streptococci play a minor, not a primary rôle, or no rôle at all, in which case the antibody reactions thereto must be nonspecific.—Ed.)

## TREATMENT OF ATROPHIC ARTHRITIS

*General Remarks.* Atrophic arthritis is a generalized disease requiring individualized treatment. A systemic disease, "it is no more a disease of joints than typhoid fever is a disease of Peyer's patches" (Pemberton). No single form of treatment is adequate. Lacking a specific remedy, physicians have too often, like the children of Israel, wandered afar after strange gods.<sup>269</sup> Although some studies on therapy have been well controlled and have taken into consideration the natural history of arthritis and its tendency to spontaneous remissions, too many have consisted of uncritical observations of a few patients for a short time only and are of little or no value. The aggressive doubter will insist that the control method be used. "I could almost cry when I read of one case cured by drug X, knowing so well the vagaries of the disease even when untreated," so wrote one physician.<sup>438</sup> In evaluating treatment one must rely most on objective improvement, less on the patient's subjective relief. Otherwise, one will be misled by the psychic effects inherent in any measure. "An enthusiastic physician may acquire at least a temporary reputation for great skill."<sup>368</sup> Nevertheless, enthusiasm and optimism are essential; if the physician exhibits a lack of therapeutic resources his patient will catch the air of futility with resultant serious depression. In appraising the value of favorite remedies one must remember that "experts also are liable to fashions." One should not be mesmerized by a spa, a local focus, a diet, a drug, a vaccine, short-wave therapy or physiotherapy, neither should one be foolish enough to decry them.<sup>438</sup> Among the pitfalls in a study of therapy is that of the dangerous but helpful drug; its full effects must be studied so carefully, for what seems to be a dangerous drug today (e.g. gold) may be improved by further knowledge. These were a few of the useful generalizations currently expressed.<sup>59, 269, 279, 368, 438, 439</sup>

*Management of Foci of Infection.* Many regarded elimination of foci of infection the measure of first importance.<sup>279</sup> Abhorring the promiscuous removal of foci one should nevertheless insist on the radical removal of any suspicious infection.<sup>569</sup> One physician wrote sternly, "When an individual refuses to have definite foci removed, they are informed that both disease and cause are theirs to do with as they choose and are requested to seek advice elsewhere." Foci should be removed early in the disease, but Pemberton, Phillips, Holbrook and Hill considered it often necessary to raise the patient's resistance beforehand; this was done by a preoperative transfusion and periods of rest and weight-gain. Buckley sometimes noted "most remarkable improvement, even a cure" from removal of foci; occasionally a temporary exacerbation occurred.<sup>59, 531</sup> Others were not so convinced of the value of removal of foci. Miller found the reports of favorable results therefrom unconvincing. Too often removal of foci was included with other therapy, thus clouding the issue, and the value of removal of foci is too often casually assayed on the basis of letters from patients. Miller considered it unfortunate that the removal of chronic foci is consid-

ered by so many to be the first and major treatment. "This procedure has been responsible for the loss of much valuable time which might have been utilized more profitably in other directions." Fletcher suggested that some foci of infection may be merely an expression of poor health, not the cause of it; therefore arthritic patients may develop new foci during their disease. The fact that the removal of foci of infection is not followed by rapid or notable relief does not, however, invalidate the importance of their eradication. Several<sup>59, 129, 569</sup> insisted that results from removal of foci may be poor because often more than one focus is present; foci are too often imperfectly removed; indeed it is practically impossible to eradicate them completely as many "foci" are not local but diffuse (for example, nasopharyngitis), and joints themselves may be foci. Lastly too much is expected of removal of foci in the presence of irreparable articular pathologic change.

As in other things, there are fashions in foci and the literature mirrors these changing fashions. Many who advocate eradication of foci will one year pounce on the prostate, another year on sinuses and so on. One physician "had yet to see a case of arthritis from sinuses, gall-bladder, colon or prostate"; his own favorite focal enemy was situated elsewhere.

*Teeth.* No more than two infected teeth should be removed at a time (O'Brien). Only infected teeth should be removed; too often the wholesale removal of teeth to "clean up the mouth" causes serious nutritional difficulties for the edentulous patient.

*Tonsils.* These came in for very little notice.

*Sinuses.* Littell stressed the frequency of "silent sinusitis" especially in ethmoids. Surgical treatment of sinusitis was applied in 20 cases of atrophic arthritis; 2 patients were unimproved, 3 slightly improved, 15 markedly improved.

(Surgical operations on symptomless sinuses should be done only after much deliberation and when done their effects should be most cautiously appraised. Only the most carefully controlled observations can determine whether or how often such a procedure is justified.—Ed.)

The importance and frequency of the *nasopharynx*,<sup>52</sup> *cervix*<sup>164</sup> and *prostate*<sup>155</sup> as foci of infection were stressed. One writer<sup>546</sup> regarded the *gall-bladder* as a focus infected more often than suspected. "Removal of bile through a duodenal tube may show that the gall-bladder is a carrier of streptococci, although the patient has no definite symptoms of cholecystitis."

(The isolation of streptococci from a duodenal tube after so-called duodenal drainage is not sufficient evidence to consider the gall-bladder infected. Recent statistics<sup>245, 247</sup> indicated the rarity of cholecystitis as a focus in atrophic arthritis and the rather unimpressive effects of cholecystectomy in this disease, even when markedly infected gall-bladders were removed.—Ed.)

Blake reported the case of a woman with epilepsy and atrophic arthritis of seven years' duration; spectacular recovery from both arthritis and epilepsy followed an appendectomy for acute *appendicitis*.

(It is difficult to believe that the appendix was a focus here or that appendectomy had a specific effect. Similarly dramatic effects not infrequently result after any surgical operation from the effects of the anesthetic, the operation and hospital rest and regimen.—Ed.)

*Vaccines.* From the standpoint of literature this was not a very good year for the cause of vaccines. Wyatt, Hicks and Thompson administered to 240 patients with atrophic arthritis intravenous injections of an antigen from nonhemolytic streptococci. A marked or definite improvement was noted in 85 per cent, increased agglutinins in 80 per cent. Sedimentation rates were favorably affected. It was admitted that other forms of treatment were coincidentally applied and that no control series was set up. Davidson and Goldie gave very small doses of hemolytic streptococcal vaccine intravenously "with apparently successful results in some cases." No other data were given. "Fairly encouraging results" were noted by Lecklitner who used Crowe's *Micrococcus deformans* and polyvalent streptococcus vaccine in conjunction with other measures. Autogenous vaccines made especially from nasopharyngeal bacteria to which skin sensitivity was evident were used by Breuer. The "most amazing and apparently ridiculously small" doses were used: 100,000 or even 1000 bacteria might give no relief or even make the patient worse, but the use of 100 or even 50 bacteria "will produce remarkable results in a few hours." Using "specific autogenous vaccines" of streptococci or staphylococci or both cultured from various foci by the pathogen-selective method, Murphy noted relief in some cases even when staphylococci were used alone. Greer treated 50 cases of atrophic arthritis with "very small doses" of autogenous vaccine alone or autogenous and Crowe's vaccine given intravenously. A total of 88 per cent were improved. He considered the intravenous route superior to the subcutaneous one, since only 55 per cent of a former series of patients treated subcutaneously were benefited.

(The fact that in 15 of the 50 patients only one joint was affected makes one wonder how many of the cases were of atrophic arthritis.—Ed.)

Some patients with persistent arthritis who were hypersensitive to streptococcal vaccine were found by Hitchcock to have staphylococcal sinusitis and to be hypersensitive to staphylococcal vaccine also. In 9 of 16 such patients the arthritis was benefited by the alternating use of staphylococcal toxoid and vaccine.

Comparing the results from different vaccines variously administered, against a control series, Holbrook and Hill were unable to prove vaccines of definite value. Nevertheless they continued to use them in some cases because of the clinical impression that certain cases were helped. With others they condemned the indiscriminate use of vaccine as a "specific remedy" to the neglect of other therapy. Doubtless many patients are somewhat benefited, but as Irons put it, vaccines are too often used as a sort of "occupational therapy" by the patient and the physician anxious for "some-

thing to do." Much of the previous work on vaccines was criticized by Kovacs because there were no controls; no routine assay of the activity of the disease was made or noted; sometimes the courses of vaccine were so long that spontaneous remissions could have occurred; usually additional therapy was given. Reports on vaccines have been given by (1) those who noted excellent results in either atrophic or hypertrophic arthritis, (2) those who noted some results but only in atrophic arthritis and in conjunction with other therapy, and (3) those who noted no better results from vaccine than from other measures. Kovacs gave various vaccines to 100 patients with "chronic arthritis." Although 30 to 40 per cent of each group noted some relief, controls treated by saline injections were similarly relieved.

According to Buckley,<sup>59</sup> vaccines often do more harm than good. Desensitization, not immunization, should be attempted; reactions should be avoided. Best results were from progressively *smaller*, not larger, doses. Others considered them "of doubtful value," "not routinely justified."<sup>181</sup>

<sup>491, 433, 546, 548</sup> Holman expressed his opinion of them as a bacteriologist. Nobody knows how they work; not even their most enthusiastic advocates. It is impossible to evaluate them but there is little or no evidence that they are "specific." Using them, we are treading on uncertain ground. "When we think we are immunizing, we may be desensitizing, and when immunity peters out we may then have an unexpected sensitization. We are playing with a dangerous weapon in a confused field. . . . If I had arthritis, I might—but I doubt it—run the risk of interfering with the little understood balance of sensitivity and immunity by the use of vaccines or other suitable antigens if I were at all sure which were the responsible microorganisms in my case."

(It is difficult for a physician or layman without arthritis to say what he might or might not do were he to develop progressive atrophic arthritis. Methods of treatment which seem quite unjustified, even risky, to the unaffected, frequently will be welcomed enthusiastically or endured philosophically by the sorry victims of this disease. Although the patient's willingness to try anything does not release his physician from the necessity of adopting a critical and judicious attitude on any therapy proposed, the stubborn nature of the disease gives the harassed physician the right in individual cases to institute cautiously such therapy as vaccines, provided both the physician and the patient appreciate the difficulties involved and exercise care to avoid harmful reactions.—Ed.)

*Foreign Protein.* Reviewing an experience of 20 years with triple typhoid vaccine injections, Miller noted that about 40 per cent of patients so treated had been entirely relieved from pain and tenderness after receiving three to five injections given once every other day. Within a month, 50 per cent (of the 40 per cent) had a return of their disease. Most of the remainder had a return of the disease after several months, perhaps a year. A few had no recurrences in five to ten years. The earlier in the disease they are given, the better the results.

*Venom Therapy.* Of patients treated by Mackenna with bee venom



("apicur") many were benefited, but since other treatments were given coincidentally it was impossible to say what caused the improvement. Beck noted "surprisingly successful results" in the treatment of an unstated number of patients with "arthritic and rheumatoid ailments" with bee venom, the hemorrhagic effect of which presumably produced an increased tissue oxidation. No physiologic or clinical data on cases treated were given. A 75 year old woman with chronic "hypertrophic" polyarthritis developed a severe allergic reaction from the sting of a wasp. Six weeks later she reported to Lincoln that her arthritis had been improved greatly since the wasp sting. She had not been so agile in years and was practically free from pain. The effect persisted for four months; then crippling returned.

*Diets.* Although the arthritic patient still wants a special diet, the disease usually does not need one; that is the current opinion of most rheumatologists. Less is being written in favor of restrictive diets and special food combinations. As Swaim said, until we know more about the disease we must be rational about diets for it. "The patient does best on that diet which would be selected for him if he had no arthritis" (Holbrook and Hill). If the patient is underweight these authors prescribe a high-calorie high-vitamin diet with no limitation of starches. Later, a high-vitamin weight-maintenance diet, low in starch, is given "not because starch is harmful but the starch eater will seldom eat enough food containing vitamins and minerals." The majority<sup>59, 279, 548</sup> prescribed a high-calorie, high-vitamin diet except for the obese. A daily minimum of 50 to 75 gm. of protein should be taken.<sup>181</sup> Others<sup>222, 431</sup> still curtail carbohydrates, but Bowen and Lockie noted no harmful effect from diets rich in carbohydrates (420 to 500 gm. daily) given to 8 patients with atrophic arthritis for 15 to 65 weeks. Joints were neither worse nor better, but general nutrition was improved. On empiric grounds, Hare prescribed a raw vegetable diet to four patients with atrophic arthritis. Only raw foods were given for two weeks; then cooked foods were added. Two patients were not improved; two improved somewhat for five weeks. Sedimentation rates were unaltered. Relief obtained was ascribed to the diet's low sodium content producing marked fluid loss.

(No laboratory or clinical data to prove this were included.—Ed.)

For reasons noted, Forbes and coworkers prescribed a high-sulfur low-carbohydrate diet: 20 of 22 patients were "markedly improved"; two were not improved.

*Additional Intestinal Therapy.* The general principles of gastrointestinal hygiene for arthritics were noted by Pemberton, Fletcher, and others. For those with achlorhydria, hydrochloric acid was prescribed.<sup>181, 546</sup> Salol was used by some. Colonic irrigations were considered useful by some,<sup>107</sup> \* of no value by others.<sup>269</sup> Adequate elimination is best promoted by proper

diet, abdominal exercises, massage, habit-time and not by cathartics. Breuer permitted small doses of magnesium sulphate before breakfast.

*Vitamins.* Various vitamins were prescribed by those who regard vitamin deficiency as a contributing or predisposing factor. Vitamin A, generally as cod liver oil, was considered most useful, especially in winter.<sup>59, 181</sup> Vitamin B, in brewer's yeast or wheat germ, was advocated by others.<sup>181, 269</sup> Live yeast should be avoided; a few cases of toruliasis therefrom have been reported.<sup>52</sup> Fletcher used generous amounts of orange juice and grapefruit juice to supply vitamin C, but no striking benefit accrued to a group of patients to whom Holbrook and Hill gave intravenous injections (150 mg.) of crystalline vitamin C three times a week for several months.

After the method of Dreyer and Reed (1935) massive daily doses (150,000 to 250,000 U.S.P.X. units) of vitamin D (concentrated viosterol) were given by Vrtiak and Lang to 20 patients for 1 to 12 (av. 3) months. Two patients showed marked, six moderate, four slight and eight no improvement. Results were not unlike those from other methods of treatment. Undernourished and anemic patients improved least. Roentgenograms in five cases before and after treatment gave no change in bone density. Signs of toxicity developed: nausea in all, frequency of urination and nocturia in a few. The series of cases was too small for an evaluation of vitamin D "but is sufficient to indicate [the need for a] conservative attitude" toward it. Vitamin D concentrate (Ertron) in daily doses of 200,000 to 600,000 U.S.P. or International units was given by Livingston, alone to five patients, with fever therapy to nine other patients. Improvement was noted by four of the first, eight of the second group. Fever therapy plus vitamin D seemed to cause more rapid improvement than either alone. Toxicity was noted frequently; nausea, urinary frequency, lassitude, anorexia, polydipsia, diarrhea, severe gastrointestinal pain and vomiting. When toxic symptoms appear, administration of the drug should be discontinued at once for one to two weeks. Brewer's yeast was ineffective in preventing or ameliorating toxicity. In some cases improvement was not noted for from one to three months. Medication was continued indefinitely until maximal benefit was noted. Blood and urine calcium and phosphorus were unchanged. There was a right shift in Schilling hemograms, a decrease in sedimentation rates. Holbrook and Hill gave 200,000 to 350,000 units daily for four months to 25 patients: in five there was less pain, in four a marked drop in sedimentation rates. Irons expressed doubts as to the wisdom of giving vitamins in large doses to cure arthritis. "Neither is an immediate favorable effect on joints clearly proved, nor have the more remote and possibly unfavorable effects of massive doses of vitamin-concentrates on human tissues been determined."

Chronic hypercalcemia was produced by Fang and Miltner in albino rats by prolonged (six or more weeks) administration of large doses (2 to 5 mg. daily) of irradiated ergosterol. Those on 2 mg. daily showed weight gain

and no pathologic change. Those on larger doses developed marked skeletal decalcification with early cystic changes, metastatic calcification in heart and various blood vessels, and calcification of extra-articular collateral vessels of knee joints. Cartilage of knee joints and of intervertebral disks showed areas of degeneration and calcification—changes not unlike those of early human degenerative arthritis. There were no histologic changes produced in parathyroids to support the contention that vitamin D acts through them. Some of the rats which had developed hypervitaminosis were put back on a normal regimen, their tissues examined later. No histologic changes were visible, indicating that rats may recover completely from the effects of prolonged feeding of vitamin D within two to three weeks after the drug is withdrawn. Large doses of vitamin D produce a marked calorogenic action in normal dogs and rats. In thyroparathyroidectomized dogs, however, such doses produced no marked augmentation in metabolic rates; therefore Deutsch, Reed and Struck concluded that the thyrotropic effect does not concern parathyroids.

(Two of us, C. H. S. and P. S. H., have given 250,000 to 600,000 U. S. P. units of concentrated vitamin D to about 25 patients with atrophic arthritis, the drug being given daily (except for occasional short interruptions) for one to two years. Cures were not obtained; articular lesions were generally altered but little, but some of the patients noted reduction in pain and soreness and increased well being. Toxicity was frequently encountered and was inadequately controlled by brewer's yeast. Two instructed patients carelessly ignored signs of early toxicity and continued use of the drug one to three weeks longer. Their severe headache, anorexia, vomiting, weight loss, transient uremia and hypercalcemia promptly disappeared under appropriate treatment. When smaller doses were used toxicity did not appear.—Ed.)

*Transfusions.* Holbrook and Hill regarded transfusions as a valuable adjunct in treatment. In chronic cases no results were noted. In acute and subacute febrile cases, "good, sometimes dramatic results" were obtained, fever and swelling subsiding. The first two transfusions were given a week apart, later ones as necessary.

(It is particularly difficult to evaluate measures used in acute and subacute cases because more or less rapid diminution in inflammation is almost inevitable regardless of what is used besides rest and physiotherapy which the patient's joints generally demand.—Ed.)

*Medicines, Miscellaneous Substances.* Intragluteal injections of leukocyte concentrate were given by Hartung and Straub to ten patients for 3 to 40 weeks. None were cured; six noted symptomatic improvement. Blood counts and sedimentation rates were unaltered.

Insulin provides a "metabolic fillip" of value in debilitated cases with weight loss and anemia.<sup>164, 222</sup> Ellman used 5 units daily the first week, an additional 5 daily units each week to a maximum of 30 units daily (15 units B.I.D.). Insulin was given 20 minutes before the principal meal, which was followed in 3 hours by glucose or a glass of milk to avoid hypoglycemia.

The trend is away from drugs since most of them have not justified

themselves.<sup>279</sup> The fashion has now changed from arsenic and iodides to gold and sulfur; Fletcher doubted whether the change represented an advance. Gutman listed scores of commercial preparations and their supposed indications. Thyroid in small doses was prescribed for those with low metabolic rates as incidental, not as specific therapy.<sup>52, 181, 548</sup> Cinchophen was considered a useful, reasonably safe analgesic by some.<sup>503</sup> Rawls considered the use of amidopyrine safe in young arthritics, unsafe in patients with long standing atrophic arthritis or in elderly patients with hypertrophic arthritis. Of 400 patients with different diseases who received variable amounts of the drug, four (1 per cent) developed agranulocytosis of whom three died. Two had long standing atrophic arthritis; two had hypertrophic arthritis. A study of the effect of prolonged doses of the drug on 100 arthritic patients (44 with atrophic, 66 with miscellaneous arthritides) was made; none developed agranulocytosis or apparent changes in leukocyte count. Breuer regarded amiodoxyl (ammonium-iodoxy-benzoate) "merely a fad which has just about passed out." Unfortunately, at least, six patients passed out with it; case reports of their deaths were collected by Hamilton whose results with it were "so poor that it has been long since discontinued." Macht and Mayo recommended bromsalizol (mono-brom-saligenin) as a superior analgesic. Quick relief of pain results from the use of rhodan-calcium-diuretin, according to Zaki. The Ru-Mari arthritis cure was exposed as an alkaline nostrum.<sup>62</sup>

*Sulfur.* Having found colloidal sulfur and such sulfur-containing substances as contramine and iodolysin of no value Krestin gave "sulfosin" (1 per cent suspension of sulfur in oil) intramuscularly every five to six days. Febrile reactions were induced in 40 patients with varying degrees of bony change: "good results" (no symptoms, normal motion) were noted in 18, "considerable recovery" in nine, partial recovery in eight, no improvement in five. Relapses within 4 to 24 months appeared in 25 per cent. "Recurrence is not surprising, since there is no reason to believe that intramuscular sulphur affects the cause." It should not be given in the acute phase (exacerbations resulted), to elderly, feeble, or emaciated patients; to nervous, hysterical patients; to the very obese (they don't stand it well), or to those with tuberculosis or other "active organic disease."

(The cases were not well classified. Some patients were hospitalized with bed rest. No control group was studied. Relief may have resulted from febrile reactions.—Ed.)

Ellman also recommended "sulfosin" reactions. Breuer's results (not given) with colloidal sulfur given intravenously were "favorable in a small number of cases." Results of Holbrook and Hill with "sulfur injections" were "disappointing."

Gates considered sulfur "a forgotten remedy" worthy of reinvestigation. "I have given sulfur in [arthritis, etc.] when there was no indicanuria. After giving it there was an abundance of indicanuria and the patient was

greatly relieved." The presumed virtues of a diet rich in sulfur were noted by Forbes and associates. Miller concluded that no report to date contained suitable controls or careful objective studies of reputed improvement. Periods of treatment were long enough for spontaneous remissions to appear.

*Gold Salts.* The treatment of arthritis by gold salts was instituted about 10 years ago. British writers now speak of it as "very valuable" (Slot), "a therapeutic measure of the first order" (Baker), "the most important form of treatment for arthritis" (Hartfall and Garland). According to Tegner: "It has always been regarded as unfortunate in Europe that the claims of chrysotherapy in the treatment of certain types of chronic arthritis have been virtually disregarded in America." If claims made for it are true, we probably deserve this chiding because until now no formal American report on the value of gold has appeared.

The mode of action of gold in arthritis is unknown. Intramuscular injections of gold are easier and as effective as intravenous injections<sup>240</sup>; oral administration seems ineffective.<sup>14</sup> Most workers now confine its use to atrophic arthritis. Bach considered it useful in any "rheumatoid type of arthritis" with proliferative synovial reactions including gonorrheal and tuberculous arthritis. It is said to be equally effective at any stage of atrophic arthritis but of limited value in spondylitis ankylopoietica.<sup>14, 18</sup> (In hypertrophic arthritis it is somewhat useful according to some,<sup>498</sup> useless according to others.<sup>14, 18, 59</sup> It is said to be useless in rheumatic fever, muscular rheumatism and gout.)

The drug is given in courses with free periods between, much as in the chemotherapy of syphilis. Injections are given every few days; initial doses varying from 0.05 to 0.1 gm., the dose usually being gradually increased. Differences of opinion exist on what constitutes one course: it was variously limited to a total dose of 1 gm. (Hartfall and Garland); 1.0 to 1.5 gm. (Buckley); 1.2 gm. (Slot); 1.5 gm. (Phillips); 1.8 to 2.4 gm. (Williams); 2 gm. (Baker); 2.5 gm. (Bach). Copeman's course for children totalled 0.25 to 0.50 gm. Rest periods between courses varied: four to eight weeks<sup>14</sup>; two to three months<sup>59</sup>; three plus months<sup>240</sup>; six months.<sup>18</sup> The number of courses necessary for results varies; the majority believed that at least two courses were necessary and that many failures or relapses resulted because subsequent courses were not given. Bach gave courses intermittently for 6 to 24 months.

The management of such therapy includes frequent analyses of urine, blood counts and sedimentation rates to gauge progress and dosage and to avoid reactions if possible. If after six to eight weeks of injections the sedimentation rate is not falling, a larger dose or a new preparation should be used, or one should stop the therapy.<sup>14</sup> Progress is slow; results may not be noted until after 8 to 12 injections. Various gold salts were used: allochrysine, sanocrysin, solganol B oleosum, myochrysine, myoral, crisalbine, lopion.



Reactions were numerous, some incidental, others more serious, some fatal. Reactions at the site of injection were usually avoided by local massage. Focal reactions, joint pains for several hours, occurred in 5 per cent of Bach's cases. General reactions—fever, increased joint pains—occasionally occur, in which case the dose should not be increased. Toxic reactions were uncommon according to some, unfortunately common according to others, "considerably more common than most of us care to admit" (Crosby). They involve many tissues: skin was commonly affected (in 5 to 10 per cent of cases<sup>14</sup>), with erythema, exanthema, papular eruption, desquamation, soreness, morbilliform rashes, urticaria, and occasionally serious exfoliative dermatitis, cases of which were seen.<sup>14, 123, 240, 575</sup> If skin reactions were local, courses were not interrupted; if general, treatment was interrupted.<sup>14</sup> Other tissues frequently affected were eyes (conjunctivitis), mouth (metallic taste, anesthesia of tongue, transient loss of taste, dysphagia, sore tongue and gums, ulcerative stomatitis), gastrointestinal tract (weight loss, nausea, vomiting, epigastric distress, diarrhea, rarely rectal spasm), liver (hepatitis, jaundice, rarely acute yellow atrophy),<sup>498</sup> respiratory tract (cough, "gold bronchitis"), kidneys (generally mild, transient albuminuria; occasional uremia), central nervous system (one case of persistent eighth nerve deafness<sup>14</sup>), hematopoietic system (epistaxis, purpura hemorrhagica, aplastic anemia, agranulocytosis). While affections of other tissues may be serious, those of the hematopoietic system are most serious, occasionally fatal. Serious agranulocytosis and fatal purpura hemorrhagica were noted by Bach, fatal aplastic anemia by Hartfall and Garland. Additional toxic symptoms were headache, dizziness, tinnitus, sleepiness, fever, general malaise.<sup>432</sup> When administered intravenously (which is not necessary) shock and pulmonary edema have been noted.<sup>498</sup>

Careful investigations of these toxic manifestations were made, notably by Hartfall and Garland, and by Crosby, reactions being analyzed in relation to many factors, individual and total dose, type of salt used, age and condition of patients and so forth. Williams and Bach believed that much toxicity could be avoided by the coincident injections of calcium gluconate but Crosby doubted its efficiency, and Hartfall and Garland noted no significant reduction of toxic manifestations. Others believed risks could be lessened by use of liver extract or glucose. Patients were warned to complain of any unusual sign or symptom. If eosinophilia of 7 to 8 per cent or more was noted, smaller doses were given.<sup>498</sup> Contraindications to such therapy were arthritis with acute or chronic nephritis (since 75 to 80 per cent of the gold is excreted by kidneys, the rest by stools), diabetes, congestive heart failure, blood dyscrasias, hepatic insufficiency; possible contraindications were marked debility and hypertension. According to some, hypertension, age and arteriosclerosis are no contraindication.<sup>18, 240</sup>

(Original papers should be consulted regarding prevention, amelioration and treatment of these complications and the plan of dosage for the various salts.—Ed.)

Results of treatment follow: Hartfall and Garland who previously reported results in 100 cases, have reported results in 300: 8.3 per cent were "apparently cured" (complete freedom from pain and disability other than that due to bony ankylosis); 69 per cent were markedly improved (some dramatically relieved); 15 per cent slightly improved; 5.6 per cent not improved; 0.3 per cent (one case) made worse, and 1.3 per cent died (four cases). [These deaths include the three noted in their first series, and one additional death from aplastic anemia.] Various preparations were used: crisalbine, solganol B oleosum, lopion, myocrysin. They saw "results which were little short of miraculous in patients showing the severest grades of disability, and a number of those previously bed-ridden became ambulatory, while others discarded their crutches and sticks." Also noted were improved general health and appetite, weight gains, reduction in sedimentation rate. Statistics indicated more cures, also more toxic reactions from crisalbine, to avoid which smaller doses than formerly should be used: present initial dose 0.05 to 0.1 gm.; maximal single dose 0.1 gm.; maximal dose for 1 course 1.0 gm.

Allochrysine was used by Baker "with uniformly good results" in an unstated number of cases. Copeman reported two cases of Still's disease "cured" by allochrysine, which was also given by Crosby to 27 patients with chronic (generally atrophic) arthritis with these results: nine greatly improved, eleven improved, three slightly improved, four not improved. Crosby concluded (1) that gold therapy is "quite the most potent now available" but (2) it is "attended by not a little risk" and "should only be undertaken when the case is severe enough to warrant such a very real risk which should be explained to the patient before treatment is instituted."

Solganol B oleosum was used by Bach and Slot. Bach stated that in early cases "a complete 'cure' may follow with full restoration of function." Half of his (unstated number of) cases "responded well" and the disease became "arrested" after treatment for from three months to two years. Of Slot's twelve patients nine improved "satisfactorily," two failed to respond and one patient ceased treatment after a reaction. Ellman treated 24 patients with "infective arthritis" with gold (solganol B oleosum) and 14 control subjects with almond oil. Both groups noted a beneficial effect but especially those on gold. Three of the latter, but none of the controls, were cured. The sedimentation rate sometimes rose the first month, then began to sink to normal and remained there, whereas in controls it was variable, dropping only temporarily. Tidy noted "undoubted improvement in several cases" but results were difficult to evaluate. F. G. Thomson considered it "of doubtful value." (No data were presented.)

American rheumatologists have certainly been "off the gold standard"; until recently the only comment was that of Cecil (1934) who briefly dismissed his results as "not striking." Holbrook and Hill simply said that their results in an unstated number of cases were "disappointing." Brief reports by Oren and Phillips have appeared. Of 66 patients treated by Oren with a water soluble gold salt 60 "responded very well." Results were en-

couraging because of the rapid response to treatment, the slight pain connected with the therapy and the lack of systemic reactions. Five or less courses were given. Phillips treated nine patients with myochrysine; only two were subjectively improved. Because of frequent toxic reactions, initial doses were reduced to 0.01 gm. He concluded that even with small doses the untoward reactions "constitute a hazard which should make us extremely cautious . . . . Personally I do not, for the present at least, feel competent to handle this drug to the advantage of the patient."

(Phillips treated 20 patients: nine with atrophic, eight with hypertrophic arthritis, two with peripheral neuritis, one with subdeltoid bursitis. Of the group only six received a total of 1.50 gm., the amount which many regard as the effective minimum. Tegner, criticizing this report, stated that Phillips' selection of cases was poor:—"more than half of his series could, in France and in this country [Great Britain] be regarded as unsuitable for chrysotherapy. . . . One can hardly feel that chrysotherapy has had a fair trial in the United States." Miller's main objection to past reports was the lack of controls in practically all of them. This objection seems valid. Apparently definite benefit results from such therapy in an impressive number of cases, but until more controls are set up we will not know the exact value of the method and how fully justified one is to run the risk of the frequent and rather serious toxic reactions.—Ed.)

*Vasodilators: Histamine, Choline.* Subcutaneous injections of histamine acid phosphate were given at first daily, later two to three times weekly for four weeks by Eastwood to 70 patients (27 with atrophic arthritis, eight with osteo-arthritis, five with fibrositis, three with spondylitis, two with gout, 25 "indeterminate and mixed"). Results were analyzed for the whole group: 74 per cent improved, 26 per cent did not. Patients with early atrophic arthritis complicated by vasomotor changes did best. Worst results were in those with no circulatory disturbance. Results were analgesic and psychologic, not curative. Transient relief from pain, stiffness and vasomotor changes were noted. "Although transitory, an immediate response of this type is of value inasmuch as it shows a patient that his condition is not hopeless, that his pain can be removed, that freedom of movement can be restored, so an optimistic state of mind is produced." Shanson noted similar results: "sometimes dramatic and lasting; often transient and disappointing." Side-actions were noted: flushing, headache, sense of warmth, drowsiness, slight fall in blood pressure. Mackenna preferred histamine ionization. Although other types of rheumatism were affected, patients with atrophic arthritis were not relieved; some were made more uncomfortable. The method was discarded for that disease. Mecholyl (acetyl-B-methylcholine chloride; formerly called mecholin) iontophoresis was applied by Mathae to 32 patients with atrophic arthritis; 72 per cent had "good results." It is not a cure but an adjunct. Phillips gave 103 treatments with mecholyl iontophoresis to 20 patients with atrophic arthritis; only two were "improved." It was abandoned as useless. Mecholyl in doses of 50 to 1500 mg. taken orally is an effective peripheral vasodilator; after

its use Goldsmith noted an average maximal rise of  $5.8^{\circ}$  C. in skin temperature of digits. An adequate dose (1000 to 1500 mg.) could be repeated every few hours to maintain vasodilation. Histamine was considered useful in early atrophic arthritis by Buckley, of unproved value by Tidy.

*Rest and Movement.* Wide approval of the principles of physiologic and mechanical rest was expressed.<sup>179, 239</sup> Rest was called "the keynote of therapy,"<sup>59</sup> "the inevitable price of recovery."<sup>52</sup> Many extra hours of bed rest are necessary for the fatigued body as well as the joints of the arthritic.<sup>223, 431, 529</sup> Inflamed joints should be put at rest in light plaster casts or splints.<sup>59, 60</sup> Fisher preferred light metal adjustable splints to plaster of paris which has certain disadvantages; it imposes a further handicap on an already poor circulation of the rested part, excludes light and air, prevents easy application of physical therapy and impedes such active, painless motion as the patient may attempt. Kindersley and Burt favored complete immobilization of an inflamed joint for one week in a plaster cast, which is then bivalved and used as a splint. Many will agree with Buckley<sup>57</sup>: "The idea that arthritics should be kept on the move lest their joints 'set' is responsible for much unnecessary suffering and has caused more crippling than it has prevented." Although a prescription for rest is vital when joints are markedly inflamed, as inflammation subsides rest for joints must not be complete lest permanent fixations occur.<sup>181</sup> Active and passive painless motion must be encouraged and increased as possible.<sup>480</sup> Swaim described the postural and bed exercises which form the optimal combination with rest. Ghormley reminded us that synovial pannus grows over parts of the joint which are not in contact; if motion can be preserved, prevention of the growth of this pannus may be partially accomplished.

*Physical Therapy.* In the treatment of the various rheumatic diseases, especially atrophic arthritis, physical therapy is widely recognized as "of supreme importance."<sup>164</sup> Thousands of crippled arthritics spend hundreds of thousands of dollars hunting vainly for the "elusive focus" or the medicinal "cure" but spend little or no effort or money on worth-while physical therapy. Other thousands contribute an annual income of \$105,000,000 to the quacks and irregulars licensed by the states to practice the physical methods too many physicians ignore (Hibben). Kling complained that physicians are now apt to over emphasize the systemic phase of the disease to the extent that they forget to treat the joints as well as the patient, and sometimes even forget to examine the joints. On the tenth anniversary of its origin the Council on Physical Therapy of the American Medical Association noted the present status of physical therapy in this country, outlining principles which should be understood by all physicians concerned with the arthritides. This and other current reports review the therapeutic rationale and physiologic effects of various types of physical therapy for rheumatism.<sup>117, 153, 322, 324, 448</sup> In Fletcher's opinion physical therapy "deserves the reputation it gained in Europe, not the neglect it has won on this side of the Atlantic."



There is a growing appreciation of the importance of teaching arthritic patients home physiotherapy. Seventy-five per cent of arthritic patients questioned by Hensch<sup>248</sup> had previously consulted osteopaths or chiropractors, because their physicians had given them no physiotherapy, or given it haphazardly, "not enough to relieve," or because physical therapy in the physician's or professional physical therapist's office was too expensive, more costly than they could get it elsewhere. The "physical therapy high-brow" may scorn simple home procedures and consider it beneath his dignity to teach his patients the simple adjuvants which would sustain the effects of professional methods. But they are a lot better than nothing and fill the need felt by the patient who has sought relief from a hot bath, a strip of flannel and a hot iron, a farm oven or a bag of heated sand, salt or oats. If his physician does not tell him of better methods he will continue his amateur efforts or get cheap help from cultists. Noting the short sighted attitude of those who insist on "all-professional physical therapy or none" Coulter outlined the simple principles and methods available for the patient's home as well as the physician's office. Others also considered of the greatest importance the formulation and use of suitable methods for inexpensive physical therapy: simple apparatus for heating; methods for passive, assistive and corrective exercises, and for massage.<sup>269, 279, 280, 548</sup>

Many recognized the advantages of *hydrotherapy* and *balneotherapy* but disagreed sharply with the point of view of those spa physicians who seek to create an attitude of superior virtue for the water of a particular spa and who, perhaps to make the patient feel dependent on the spa, make no effort to teach the departing patient home physiotherapy in order to project into the patient's home environment at least some of the benefits of the spa. Miller conceded that spas provide superior opportunities for rest and relaxation and have a psychologic effect "but the water has no more value than that in the home bath tub." In Tidy's opinion "few of the so-called researches from spas have fulfilled the canons of scientific evidence and research." Many spas with widely different waters and climates produce the same results. Unless something more definite, or something common to many spas can be produced with scientific support, the profession and the public may decide the various claims cancel out and that the maximal benefit from therapy can be obtained without visiting a spa." There being no evidence that any ingredients of the water, peat or mud are appreciably absorbed by the skin, results must come from other factors—heat, rest and so forth. Some consider the ordinary hot bath at 100° to 120° F. for 20 to 40 minutes the most useful form of heat.<sup>560</sup> "Electric pads and hot water bottles are a joke; they produce no real benefit." Ellis favored the *Wilde hot bath*. *Ultra-violet* rays as the sole therapy are ineffectual, according to Pringle who favored hot *paraffin wax baths*. *Faradic currents* help to control muscle wasting.<sup>548</sup>

*Conventional Diathermy; Short-Wave Diathermy.* Ordinary or "long



wave" diathermy utilizes wave lengths from 100 to 400 meters (theoretically from 30 to 500 meters, but no machines currently use wave lengths below 70, few below 100 meters). "Short-wave diathermy" (the Council-approved term synonymous with "short-wave therapy," "short-wave high frequency," "radiotherapy," "radiathermy"), concerns wave lengths from 12 to 30 meters. "Ultra short-wave diathermy" (synonymous with "ultra short-wave therapy," and so on) utilizes waves of 3 to 12 meters in length. In current dispute are arguments that short-wave and ultra short-wave diathermy are therapeutically superior to ordinary (long-wave) diathermy, that the different wave lengths in the short and ultra short range have different physiologic actions, and that short and ultra short-waves produce effects by a specific effect apart from their heating potentialities. Those interested in general and technical details are referred to several papers.<sup>111, 112-114, 425, 552</sup> Although some still believe otherwise<sup>29, 283, 284, 315, 466</sup> the majority believe results are due solely to the heating effect of short or ultra short-waves, different lengths of which produce identical, not specific, effects.<sup>113, 114, 264, 537, 582</sup> Kovacs concluded that the primary physiologic and therapeutic effects of long and short-wave diathermy are essentially the same, that burns are commonly produced by short-wave diathermy; that short-wave diathermy is technically more convenient but less efficient than conventional diathermy.

Ordinary diathermy is useful in arthritis,<sup>180</sup> as useful as short-wave diathermy<sup>537</sup> but over-rated<sup>548</sup> and often disappointing in its effects.<sup>111, 112</sup> Beneficial effects from short-wave<sup>506, 582</sup> and ultra short-wave diathermy<sup>311, 467</sup> were noted in a few cases of atrophic arthritis.

(The editors of the reviews believe clinicians in general will share their disappointment at the inadequacies of most "clinical reports" published in certain special journals on physical therapy. These reports on arthritis rarely contain data on any controls; they make little or no attempt to differentiate the various types of arthritis being treated; if they do, they contain practically no clinical or laboratory data indicating the extent or severity of the disease from which one can base an independent opinion on the value of therapy. As a rule a few representative "successes" are reported in the most cursory detail. In technical matters they are often excellent; as clinical investigations they are generally very inadequate and disappointing. The variations and vagaries of the arthritides being what they are, it is suggested that specialists in physical therapy team up with clinicians and "rheumatism specialists" to instigate those clinical investigations in physical therapy which are so long overdue.—Ed.)

*Occupational Therapy.* The importance of occupational therapy as adjuvant to older forms of physical therapy for chronic arthritis needs continued emphasis.<sup>278</sup> In the management of almost every arthritic patient there is a time or a place when occupational therapy will accomplish results peculiar to itself and more efficiently than conventional physical therapy. As Krusen, Macey and Pattee pointed out, these are not mutually exclusive or antagonistic forms of therapy; they should be correlated and interdependent, yet independent. Featuring active exercises of a specialized and often highly individualized nature, occupational therapy is a most useful

addition to the more passive types of physical therapy. In the correction of arthritic deformities Cunningham and Shimberg found it very effective.

*Roentgen-Ray Therapy.* Beneficial results from "wide-field roentgen-ray therapy" were noted by Scott in "spondylitis adolescens," but not in atrophic arthritis. Certain cases demand local radiation; others require general radiation. Deep therapy, the use of the more penetrating rays, is needed only for the hip joint; for other joint tissues more superficially situated the less penetrating rays are better. Scott stressed the importance of placing the joint under treatment in the optimal position for exposure of the full joint surface to the rays.

(No statistical results were given.—Ed.)

Tidy considered deep roentgen-ray therapy for arthritis of unproved value.

*Fever Therapy.* Effects of fever therapy in atrophic arthritis have been disappointing. Results are better in acute than in chronic atrophic arthritis. Thus, in Hench's survey of reported cases results were as follows: of 21 patients with acute atrophic arthritis, only 10 per cent became symptom free, 40 per cent were relieved. Of 147 chronic cases 10 per cent became symptom free, 25 per cent were benefited. Of 60 additional patients treated by Hench none were cured; only 20 per cent were definitely benefited. Of patients more recently treated, more than 50 per cent received little or no relief. Bierman noted temporary improvement in most cases; permanent results so rarely that fever therapy was not recommended. In the treatment of 40 patients, Stecher noted no cures, in about 30 per cent "substantial results" which were maintained 6 to 12 months. Thus, of 38 cases of chronic, and 10 of acute atrophic arthritis results were "very good" in 16 per cent and 30 per cent, good in 29 per cent and 40 per cent respectively. A fever session in acute cases was five hours at 105° F., in chronic cases three to four hours at 103° to 104° F. Short sessions of low fevers (1½ to 1 hour at 101° to 101.5° F.) were advocated by Atsatt and Atsatt as "metabolic boosts." (No results were cited.) McClure noted "satisfactory relief" in 46 per cent of 13 chronic cases. Of Neymann's<sup>405</sup> patients (not numbered) 15 to 30 per cent were greatly benefited, 30 per cent moderately relieved. Fifty patients were treated by Holbrook and Hill with "disappointing results." None were symptom free, 25 per cent were temporarily relieved.

*Climate and Clothing.* The influence of these factors was discussed briefly by Burt and by Holbrook and Hill. Natives of the Arizona desert rarely develop atrophic arthritis and arthritic visitors have few exacerbations. However, climatotherapy is not a panacea for the disease; all other orthodox measures should be used.

*Sympathectomy.* Bilateral lumbar sympathectomy was performed by McDonald in two cases of long standing Still's disease with marked swelling and deformity of many joints, muscle atrophy and cold, clammy extremities.

Thereafter the patients were more comfortable because of warm, dry legs and feet but "no obvious change was noted in the appearance or in the degree of movement of the affected joints." White recommended the operation only in cases of atrophic arthritis "when it is desirable to improve circulation per se in cold moist extremities." He had noted no relief of pain or increased mobility in five cases so treated. A patient of Bothe, affected for six years, bedridden for several months, noted gradual but definite improvement which was notable the first two months after operation and continued thereafter. Blocking the appropriate sympathetic nerves by alcohol injections was used by Patterson and Stainsby as a substitute for surgical sympathectomy. In 11 arthritic patients so treated, satisfactory increases in skin temperature were noted which persisted for an average of six months, average increases being  $11.6^{\circ}$  F. at toes,  $10.9^{\circ}$  at fingers,  $3.3^{\circ}$  at knees,  $5.6^{\circ}$  at elbows. Although symptoms of faulty circulation were definitely improved, the results for the joints were "very disappointing": two patients showed definite diminution of the arthritic process, the others showed little or no improvement.

In sharp contrast to the above were the results of Young, who performed the operation on seven severely crippled patients with atrophic arthritis with "remarkable improvement" in each. Most of them were bedridden, some with "extremely disabling polyarthritis" flexion deformities and "profound disablement of limbs." Noted very shortly after sympathectomy were "rapid relaxation of flexor spasms," banishment of pain, restored power of walking, "practically complete restoration of useful function," "rapid improvement in function of limbs, even of the most disorganized and disabled joints" (the latter comment referring to a case of eight years' duration with "marked deformities—almost complete disablement").

(In view of the past experiences and current reports of others it is very difficult to share Young's enthusiasm. Although a brief sentence on the subsequent maintenance of improvement was given in two cases, concerning others in which operation had been performed two to four years ago no subsequent observations were noted. Several of the patients noted marked postoperative improvement in upper extremities, nerves to which were not interrupted. It was not stated how long this improvement lasted. One of us (P. S. H.) has followed all results of sympathectomy for arthritis with particular care as he was associated with Rowntree and Adson from the initiation of this work (1928), indeed helped choose the first and subsequent patients treated by them. As a physiologic procedure sympathectomy for atrophic arthritis seemed rational but to those who originated and followed it from its onset it has given clinical results in the main disappointing. Adson's current comment follows.—Ed.)

According to Adson "cervicothoracic and lumbar sympathectomy have been of value only in relieving symptoms and checking the disease in a small group presenting definite disturbances of sympathetic origin, characterized by vasoconstriction and hyperhidrosis . . . . The operative treatment does not alter deformities, contractures or the condition of ankylosed joints. It

is of no value in the treatment of arthritic processes in larger joints—knees, elbows, hips and shoulders.”

*Bone Puncture (Forage).* Further favorable results from bone puncture were reported by Mackenzie. His reason for adopting this procedure (1931) was given previously<sup>245</sup>: an elderly arthritic patient, long crippled, broke a femoral neck; during convalescence her arthritis became, and remained, painless. Mackenzie's procedure was an empiric approximation of this phenomenon. He concluded that atrophic and hypertrophic arthritis (“essentially the same in origin”) are the results of primary osteitis, arthritis being secondary thereto. Treatment consisted of drilling “sufficiently large” holes in para-articular bone—in the lower end of the femur and upper end of the tibia when knees were involved; in the femoral neck, trochanter and acetabular margins when hips were affected. Some marrow is scooped out “the whole idea being to bring about a state of decompression.” In a typical case of “osteoarthritis” clear, oily fluid, “definitely under pressure,” wells up; in it are white granules often larger than the head of a pin. Cultures and microscopic examination of this material revealed “nothing of interest.” After operation convalescence was generally uneventful. The operation was done for hips or knees of 106 patients; statistical results were not given but “an improvement really worth while can be expected in 80 per cent of cases.” The cause of relief was not known.

(This procedure is not new: in 1890 Noble Smith reported good results from “bone drilling in the neighborhood of inflamed joints and elsewhere.” Similar results have been reported recently from France by Graber-Duvernay, 1932, 1933, 1935: definite improvement in seven of ten cases. Simpson and Henderson noted “lasting relief from pain” in three of twelve cases of “hypertrophic osteo-arthritis” of hips, lesser improvement in four others.—Ed.)

*Prevention and Correction of Deformities.* The well-known procedures for the correction or prevention of deformities were again reviewed.<sup>59, 239, 255, 288, 306, 368, 384, 480, 529, 530</sup> They included the use of plaster splints and braces, and various operative procedures. Discussed were the best type and safe duration of immobilization<sup>306</sup> the use of oxygen insufflation to prevent or correct adhesions,<sup>257, 259</sup> optimal positions for ankylosing joints, also for those where retention of function is anticipated.<sup>289, 480</sup> Points which cannot be too often emphasized were that with the coöperation of the physician and orthopedist deformities generally can be prevented by early treatment, or can be largely corrected once they have occurred, and that functional use of deformed joints can be restored by suitable orthopedic surgical and non-surgical procedures.<sup>179, 255, 529, 530</sup> Too often so-called coöperation between physician and orthopedist is merely a matter of lip-service; to be successful it should be vital, continued from the onset of the disease (Fisher). The various causes and types of adhesions were ably discussed by Jones: adhesions may result from too little or too much motion of joints, from uncorrected edema, from joint manipulation or over strenuous physiotherapy.

Besides the placing of pillows under knees, the "shortest route to the wheel-chair" is accomplished by the patient with painful bent knees who keeps walking no matter how much it hurts (Holbrook and Hill). When cartilaginous destruction has occurred, manipulation (active, passive or surgical) must be done with caution. Henderson stated, "If a joint is more or less fixed at a certain angle and use only changes that angle to another fixed angle, one must not manipulate it. When the range of motion is increasing one should trust to active motion; when it is not increasing, then only should passive movements be carried out, but not forcible manipulation." Manipulation under anesthesia requires more experience than any other procedure; one of the last things a young orthopedist should be encouraged to do. In an instructive paper Lewin listed 18 do's and don'ts in manipulation of arthritic joints. For the correction of flexed knees some believed posterior capsulotomy often necessary in addition to the use of manipulation and bivalved splints.<sup>57, 269</sup> Of 19 cases in which such treatment was given results were successful in 14 (Holbrook and Hill).

*Psychotherapy.* Little attention has been paid to this factor, which is such an important and (from the standpoint of evaluating clinical results) so often an unrecognized feature of any treatment scheme. It is imperative that the patient be taken into his physician's full confidence and vice versa, that the patient be instructed fully in the problems that lie ahead, that he know the limitations and possibilities of his own and his physician's therapy, that the reason for good results but particularly for the bad results (which patients see about them and inevitably remember) be frankly discussed (Fletcher, Ellman). Social, emotional and economic adjustments are often required that the patient may be properly conditioned for the prolonged treatment so often necessary for success. Both physician and patient must realize there is no easy way to a "cure." Physicians should stop treating patients half-heartedly with each new remedy of doubtful value and concentrate on the few simple measures of proved worth.<sup>269</sup>

*Prognosis; End Results.* According to Pemberton, 75 per cent of arthritic patients should experience great betterment or complete arrest; 20 per cent are more refractory perhaps because of a dominant continued infection; in 5 per cent therapy is of no avail. In Sweden a plan of hospital treatment and subsequent occupational adjustment has been set up. According to Kahlmeter, 70 to 80 per cent of patients leave the hospital fit for work. Enduring results were relatively frequent: 62 per cent of 1000 patients were earning all or part of their living three or more years after hospitalization. Other figures noted by Kahlmeter were those of Zimmer (57 per cent "definitely improved"), of a Silesian Insurance Institute (80 per cent relieved), of Danischewsky (52 per cent working) of Freund (36 per cent cured, 45 per cent improved). Of 452 generally "completely helpless" patients with atrophic arthritis discharged from the Robert Brigham Hospital, Boston, about 66 per cent of those living in 1935 were working,



21 per cent had had relapses (Kuhns and Joplin). The commonest diseases complicating convalescent care were arteriosclerosis in 41 cases, nephritis in 22, hypertension in 19, obesity in 17, myocarditis in 16, gonorrhea in 12, rheumatic heart disease in 10. There were 76 deaths; 18 from pneumonia, 13 from myocarditis, 11 from nephritis, 6 "postoperative," and 28 miscellaneous.

#### HYPERTROPHIC ARTHRITIS

*Definition.* In the following discussion "hypertrophic arthritis" means a clinical syndrome, not just a roentgenographic alteration; it is synonymous with senescent degenerative osteo-arthritis, or "primary osteo-arthritis"<sup>59, 225</sup> as contrasted to secondary (hypertrophic) osteo-arthritis which may appear as the (radiologic) end result of many articular disorders, among them gout, late atrophic arthritis or gonorrheal arthritis in weight bearing joints.

(The merits and demerits of the various terms for this disease were critically reviewed by Bauer and Bennett. The term "hypertrophic" is not satisfactory because the hypertrophic changes are a relatively late feature of the disease, much later than its degenerative feature; nor is "hypertrophic" distinctive because many types of arthritis may show hypertrophic changes; for example, gout, hemophilia, Charcot joints, and so forth.<sup>178</sup> "Senescent" is a better term and is usually, but not always, appropriate, as the disease may, under unusual circumstances, appear long before senescence. The word "degenerative" describes the primary phenomenon of the disease, is therefore peculiarly fitting and should be retained in the final designation. "Arthritis deformans" is not distinctive since other forms (for example, atrophic) may be even more deforming. The term "arthritis" has been objected to since there is little or no evidence of inflammation; hence, some have suggested "arthrosis" or "osteo-arthritis" which literally translated means "a joint full of bone." For various reasons therefore the term "degenerative joint disease" seemed preferable to Bauer and Bennett, until a term based on the ultimate etiology of the degeneration is known.—Ed.)

*Incidence.* The studies of Bauer and Bennett, and others revealed that with each succeeding decade in life beyond the second, certain joints, especially knees and joints of the spine, show "degenerative arthritis" with increasing frequency so that the disease is pathologically universal after the age of 40 to 50 although it may be clinically apparent (that is, symptomatic) in only about 5 per cent.

*Clinical Features; Symptoms.* Of Haden and Warren's 50 consecutive cases the age incidence was from 34 to 69 (av. 51) years in females, 34 to 58 (av. 52) years in males. Females were affected symptomatically five times as often as males (42 females, 8 males). In the cases which Bauer and Bennett studied at necropsy the patients had presumably never had significant symptoms although joints were often markedly affected. It is common to find marked hypertrophic changes in one joint which is practically painless, and to find only slight radiologic changes in another joint which is very painful. Why is one painful, the other not? Some believe the pain is due to superimposed infection. According to Bauer and Bennett two

factors are responsible for pain. When marginal tissue is proliferating the periosteum may become elevated and cause pain. Once the marginal osteoid tissue ceases to proliferate and becomes calcified pain may also cease. The second factor in pain production is related to altered mechanics, occasional loose bodies, or the pinching of sensitive synovial villi. Gordon, however, blamed two other factors for the pain: (1) exposure of soft subchondral bone by cartilage destruction, and (2) presence of muscle spasm from the fibrositis which almost invariably accompanies hypertrophic arthritis. Buckley reminded us that patients with affected hips often have no pain therein, pain being referred to the knees which, in spite of normal motion and roentgenograms, are sometimes long treated for arthritis nonexistent therein.

*Roentgenograms.* The characteristic and differentiating radiographic features have been discussed. Spurs and exostoses, commonly present at muscle insertions, are but the "perfectly natural strengthening of ligaments at their insertions" and should not be misinterpreted as "osteo-arthritis"—a mistake often made even by radiologists, according to Gordon, to whom the essential roentgenographic feature of hypertrophic arthritis is the presence of osteoporotic areas in or about articular bone.

*Pathology.* The well-known pathologic features were reviewed by several.<sup>194, 195, 290, 300</sup> In particular, Bauer and Bennett reviewed their development in the human and animal (spontaneous and experimental) forms of the disease.

*Laboratory Data.* Anemia is rare; only 4 per cent of Haden and Warren's 50 patients had hemoglobin below 75 per cent (11.5 gm. per 100 c.c.). The neutrophile nuclear count usually does not show a left shift in hypertrophic arthritis as it does in atrophic arthritis. But such a shift was noted by Collins in 30 per cent of 11 cases of hypertrophic arthritis of hips and seemed to bear a definite relationship to bone cysts in hip joints. Accepting Ely's view that the cysts were areas of aseptic necrosis, Collins suggested that toxic absorption of some kind must proceed from these cysts, for when they were large, that is, with a large surface from which absorption might take place, the nuclear count showed a marked left shift; when cysts were small or scarcely apparent, the nuclear count was normal. Hartung and co-workers noted that the nonfilament count, which was always elevated in atrophic arthritis, was normal in 53 per cent, elevated in 47 per cent of cases of hypertrophic arthritis "perhaps due to associated rheumatoid disease or focal infection."

In contrast to atrophic arthritis the blood proteins are essentially normal in hypertrophic arthritis (Davis). The sedimentation rate was slightly elevated in 7 of Davis' 11 cases, normal in 80 per cent of Haden and Warren's 50 cases. Fasting blood sugar levels were usually normal; 22 per cent of the 50 patients had diminished sugar tolerance.

The cytology of synovial fluid in hypertrophic arthritis is strikingly dif-

ferent from that in atrophic arthritis. Collins noted a low absolute polymorphonuclear count in each of three cases, implying an absence of synovial inflammation. Total nucleated cells per cu. mm. were 210; 900; 5800; polymorphonuclears 4.5 to 14 per cent.

Contrary to the opinion that effusion is rare, Kling found in "osteoarthritis" periodic marked increases of synovial fluid with a high viscosity and a small number of cells, chiefly monocytes and synovial lining cells, indicative of synovial hypertrophy and hypersecretion.

*Etiology and Pathogenesis.* No new views on etiology were expressed. The disease is presumably a degenerative process resulting not from one specific factor but from the wear and tear of increasing age; in other words, it is caused by life and the process of living.<sup>28, 59, 83, 181, 225</sup> It is fostered by certain predisposing factors; hastened or made symptomatically active by other factors. Current writers differed only in the individual importance they ascribed to the different precipitating factor of heredity and constitution (that is, inheritance of vulnerable cartilage) or of the following accelerating factors: abnormal metabolism, circulatory deficiency to joints, various traumas, toxemia from infection, nutritional deficiency of articular tissues, gastrointestinal disturbances, exhaustion, alcoholism.<sup>181, 225</sup> Some regarded the factor of trauma as the most important, and assigned no rôle to infection, metabolic disturbances or endocrine dysfunction (Bauer and Bennett). Others (Haden and Warren, Fletcher) stressed the importance of metabolic or nutritional factors.

*Heredity and Constitution.* Anthropometric studies by Kovacs and Hartung indicated that patients with hypertrophic arthritis tend to have increased horizontal measurements, short thick necks, massive silhouettes, chest circumferences greater than abdominal. Ellman and Mitchell found slight, Kovacs and Hartung found no, psychologic differences between patients with atrophic and hypertrophic arthritis.

Patients may inherit the tendency to hypertrophic arthritis by inheriting tissues susceptible to degeneration (O'Brien). In cases in which hypertrophic arthritis comes on prematurely it is possible that premature senescence of cartilage has set in, cartilage aging faster than the rest of the patient's tissues. Thus Bauer and Bennett suggested that the type of cartilage one inherits governs in part the age of onset of hypertrophic arthritis and the rapidity with which it develops. If one inherits "good cartilage," hypertrophic arthritis may be long delayed in spite of the operation of the usual predisposing and aggravating factors. Considering the hereditary factor most important, Haden and Warren were unable to evaluate it in their patients because family histories of "arthritis" were so unreliable.

*Trauma.* Several<sup>28, 208</sup> regarded the dominant factor to be a variety of "microtrauma," that from obesity, overuse through occupation or recreation, malposture, congenital deformities or other mechanical defects. Gor-

don saw a close relationship between juvenile disorders—congenital hip disease, coxa plana, slipped epiphysis, Perthe's disease—and hypertrophic arthritis of hips late in life. Of Haden and Warren's 50 patients with hypertrophic arthritis 62 per cent were an average of 25 pounds overweight, a source of physical strain to weight bearing joints. Bauer and Bennett particularly stressed the factor of trauma. Hypertrophic arthritis was readily produced by altering the apposition and weight bearing of joints in animals. Certain patients were found to have marked hypertrophic arthritis in one joint subject to unilateral occupational or postural trauma, but none or very little in the opposite joint. Thus hypertrophic arthritis may result in one knee more than its fellow, from loose bodies, knock knees, bow legs, intra-articular fracture, a pronated foot.

*Impaired Circulation.* Many assumed that hypertrophic arthritis may be due to deficient articular circulation, the circulation being impaired because of hypotension or, more often, of hypertension and arteriosclerosis. Buckley<sup>58</sup> noted the frequency of osteo-arthritis of hips in horseback riders due possibly not to trauma but to obstruction of the blood supply through compression of the artery of the ligamentum teres owing to extreme abduction of the hip. According to Gordon the disease occurs in those whose vascular system is beginning to deteriorate, not necessarily generally, but locally, in the region of one joint or one limb. "This vascular deterioration leads to a relative malnutrition and consequent degeneration of structures whose blood supply is defective, and this is the primary cause of osteoarthritis."

(No data proving these ideas were given.—Ed.)

Of Haden and Warren's cases none of the 8 males and only 24 per cent of the 42 females had a systolic blood pressure more than 140 to 145 mm. of mercury. Nevertheless they concluded "the frequent observation of calcareous deposits in arteries, the common finding of arterial hypertension, and the well-known gradual decrease in capillary bed with age, all emphasize the circulatory factor."

Monroe and Walcott compared 257 patients with hypertrophic arthritis to "normals" of similar age and noted the following respectively: cardiac enlargement in 18 per cent of arthritic patients, in 4 per cent of controls, hypertension respectively in 39 per cent and 8 per cent, arteriosclerosis in 16 per cent and 18 per cent, varicose veins in 15 per cent and 8 per cent. They concluded that cardiovascular disease occurs with increased frequency in patients with hypertrophic arthritis.

(The conclusion does not seem justified. Arteriosclerosis was not present in an unusual number of cases.—Ed.)

Bauer and Bennett admitted that vascular deficiency might be a factor but in the study of knee joints of persons with hypertrophic arthritis who died at various ages arteriosclerosis was not found to be an important feature.

*Endocrine Disturbances.* Some<sup>415</sup> vaguely incriminated "an endocrine

imbalance of thyroid and ovaries," but, as Bauer and Bennett stated, no proof exists that endocrine disturbances alone ever produce the disease. Of Peer's 28 cases the metabolic rate was below — 9 in 60 per cent, below — 14 in 3 per cent (below — 19 in 2 cases).

(No normal controls of similar age were studied. His results in the atrophic group were essentially similar.—Ed.)

Of Haden and Warren's cases metabolic rates were (slightly) above normal in 16 per cent, below normal for their age in 84 per cent; the average decrease below normal was 15 per cent.

(Most patients were given only a single determination. The analysis as given was not complete enough for conclusions.—Ed.)

Miller believed that endocrine disturbances may cause the obesity but not the arthritis, except indirectly.

*Metabolic Disturbance.* Peers found no disturbances of sugar metabolism of etiologic significance. Indoluria was noted by Forbes and associates in 10 of 13 cases of hypertrophic arthritis as well as of atrophic arthritis. Because of this and because five of eight patients treated with a high sulfur, low carbohydrate diet "improved," a disturbance in hepatic function and in sulfur metabolism was suspected. Six patients studied by Rinehart, Greenberg and Baker showed no evidence of vitamin C deficiency; indeed their plasma ascorbic acid content was high: 0.90 to 1.34 mg. per 100 c.c.

*Factor of Infection.* Patients with hypertrophic arthritis present little direct or indirect evidence of infection. Practically none of the patients of Haden and Warren had been seriously ill within five years of the onset of arthritis. Only 42 per cent had *foci of infection*, a small per cent for the age of the group. *Blood cultures* from 39 patients of McEwen, Alexander and Bunim were positive (all for green-producing streptococci) in 26 per cent, a finding considered incidental. Patients with hypertrophic arthritis do not often possess *agglutinins* either to hemolytic or green-producing streptococci in significant titer. McEwen, Alexander and Bunim found *agglutinins* to hemolytic streptococci in none of 46 patients. Hartung and associates noted *agglutinins* to green-producing or hemolytic streptococci practically never (in a few cases to one green-producing strain only). *Agglutinins* to hemolytic streptococci were found by Goldie and Griffiths in a dilution of 1:100 in only 10 per cent, 1:200 in 5 per cent, 1:400 or more in none; to green-producing streptococci in dilutions of 1:100 in 5 per cent; in higher dilutions never. *Precipitins* to hemolytic streptococci were present in serum of 10 per cent of 21 patients.<sup>243</sup> They were present in 18 of the 30 cases of McEwen and associates (reaction slight in seven, definite in seven, marked in four, very strong in none).

*Antistreptolysins.* More than 100 units were not present, according to McEwen and associates (46 cases), Dawson and Olmstead (24 cases), Goldie and Griffiths (30 cases). *Antifibrinolysins* were absent in all of



Stuart-Harris' six cases, in 62 per cent of 13 cases of McEwen and associates (they were weakly present in 38 per cent). *Skin tests* with hemolytic streptococci were negative in 100 per cent; those with green-producing streptococci were negative in 97 per cent of the 30 cases of Goldie and Griffiths.

In spite of this mass of negative evidence others believed that infection might play some rôle. Poynton<sup>439</sup> stated that osteo-arthritic changes may be produced in animals by injecting streptococci intravenously. Irons had seen Heberden's nodes become acutely tender, red and swollen following a respiratory or other infection. According to Holman the absence of a pathologic reaction of inflammation does not entirely rule out the rôle of infection.

*Treatment.* Since cartilage has little or no capacity for repair, little can be done to replace significant cartilaginous destruction or to "cure" the disease. But much can be done to lessen pain, perhaps to stop or slow the progress of the disease by correcting accelerating and causative factors.<sup>28, 58, 225</sup> Measures should be (1) to relieve strain and trauma of all sorts, (2) to check factors which favor degeneration. Given a chance, nature will repair many of the cartilage defects after a fashion (with fibrosis); the repair at best is a poor substitute for the original cartilage but often the joint will be as useful as ever (Ghormley). Some will be limited, a few will become markedly limited. True ankylosis does not occur but "artificial ankylosis" may result from interlocking osteophytes. Reassurance is one of the most important features of treatment; patients must be told they are not headed for crippledom and a life of invalidism.

Many of the measures indicated in atrophic arthritis, particularly the more strenuous ones, are not suitable in hypertrophic arthritis. According to Bauer and Bennett, there being "no evidence favoring infectious, metabolic or endocrine theories, these patients should not be subjected to wholesale removal of foci, administration of endless sera and vaccines, endocrine therapy, colonic irrigations, hyperpyrexia, weird dietary regimens, etc." However, Pemberton believes that measures effective in atrophic arthritis are equally applicable in hypertrophic arthritis.

Reduction of trauma of whatever type is indicated. Bed rest is often very useful, but rest should not be complete; joints should be moved through their full range of motion frequently.<sup>28, 58, 431</sup> Bandages or caliper splints may provide special rest for hips or knees, and corsets or braces for the back.<sup>58</sup> However, "it is often difficult to persuade the conservatively minded and short-tempered old lady or gentleman to harness themselves with 'this piece of damned iron-mongery'" (Gordon).

Obesity being a common source of trauma, weight-reduction diets were generally advised.<sup>28, 58, 225</sup> Two patients, given a raw vegetable diet, noted some relief at first; relapses later.<sup>237</sup>

Massive doses of vitamin D alone were given by Livingston to three patients, in conjunction with fever therapy to four other patients; two of the former and all of the latter were "improved."

Some saw no indication for removal of foci,<sup>28</sup> others removed them conservatively for general reasons. Gordon wrote, "If the physician can persuade himself that a focus of infection is contributing to the general degenerative process, then such a focus should be removed so long as the strain involved in its removal does not prove too much for the frequently elderly and sometimes feeble person, so that he dies of his cure." Kovacs gave various vaccines in 42 cases: improvement was noted in only a few; some patients were made worse. Foreign-protein therapy seemed useless.<sup>208</sup> Cases of hypertrophic arthritis were considered suitable for bee-venom therapy by Mackenna [no statistics given.]

Iodine was prescribed by Buckley, given orally or intramuscularly as lipiodol "to provide a reservoir of the drug from which absorption into the circulation continually goes on with definite relief of pain and stiffness in many instances." Intramuscular injections of sulfur gave "considerable recovery" to only two of Krestin's five patients. Sulfur, given in a high sulfur diet, "markedly improved" five of eight patients of Forbes and associates.

Gold therapy is "useless," "unsuitable" in hypertrophic arthritis.<sup>14, 18, 538</sup> Only two of eight patients of Phillips noted subjective improvement. However, Slot noted "beneficial results" in some cases, and 13 of Oren's 22 patients "responded well." Gordon regarded "the precious metal more obviously beneficial to the physician than to the osteo-arthritic patient." Histamine injections were recommended by Eastwood and Shanson, histamine ionization by Mackenna, 9 of whose 13 patients noted reduction of pain and stiffness.

Roentgen-ray therapy was considered useful<sup>164, 183, 477</sup>; it is presumably analgesic, reduces congestion, and causes absorption of pathologic fibrous tissue.

(Very few, if any, controls were used in the evaluation of most of these forms of treatment; details given were very meager.—Ed.)

*Fever Therapy.* Of 64 patients treated by Davison, Lowance and Barnett, 44 were "markedly relieved," 13 "definitely relieved" and 7 not relieved. To the "great surprise" of Warren and Lehmann "several cases" of hypertrophic arthritis were "markedly relieved over a long period of time" after a single artificial fever at 40.5° C. for 4 hours. Others considered cases of hypertrophic arthritis unsuited for fever therapy. The patients do not react well, and during such therapy may develop "delirium and other terrifying states."<sup>405, 406</sup> According to Hench's summary of reported results in 74 cases, only 5 per cent of patients became symptom-free.<sup>249, 250</sup>

*Physical Therapy.* The usual varieties were recommended. Several favored hydrotherapy,<sup>58, 104, 183, 208</sup> especially the use of warm pools; it relieves the muscle pains and spasm of associated fibrositis. Relative merits of different forms were described.<sup>58, 448</sup> Patients with hypertrophic arthritis are particularly in need of simple methods for home physiotherapy which

Coulter described. Short-wave therapy gave temporary relief in a few cases.<sup>506, 582</sup>

*Sympathectomy.* This is not indicated in senescent hypertrophic arthritis according to Adson. However, Young noted "rapid amelioration of pain" and "substantial improvement" in motion of the hip of a 62 year old woman who was so painfully crippled that she requested the procedure.

(Because of temperature gradients existing in legs, skin temperatures about hips and thighs are altered but slightly after sympathectomy. It is unlikely that in Young's case relief was due to sympathectomy per se; it was probable that from any operation, the effect of anesthesia, bed rest, convalescence.—Ed.)

*Bone Puncture.* "Osteoarthritis and rheumatoid arthritis belong to the same type of disease" according to Mackenzie, who obtained "worth while improvement" by bone puncture in 80 per cent of 106 cases (types not separately analyzed). This was discussed under the treatment of atrophic arthritis. Simpson and Henderson noted "definite benefit" in seven of twelve cases of osteo-arthritis of hips (for more than six months at time of follow-up) in which bone drilling of the neck of the femur was done; only one of ten patients subjected to trephining by Ducker noted improvement. Contrary to Mackenzie's experience, Ducker noted exacerbation, not relief, of symptoms of osteo-arthritic hips after spontaneous fracture of femurs.

*Orthopedic Procedures.* Indications for cheilotomy, osteotomy, arthrodesis, arthrotomy, acetabuloplasty, and plastic procedures on the head of the femur were given.<sup>178, 255</sup> In selected painful cases of monarticular hypertrophic arthritis of hips, Malkin noted good results from femoral osteotomy. Arthrodesis seemed most satisfactory to Gordon.

For the relief of pain in hips Slot recommended epidural injections of 1 per cent procaine.

#### BACKACHE

There have been two schools of thought as to the cause of backache. "The cause of most backaches is anywhere but in the back." According to this, the older school, pains in the back most often arise from distant infection or from gynecologic or urologic diseases. According to the newer or "mechanistic school," the cause of most backache is in the back (Miliken). Backaches are described as of medical, orthopedic, urologic, neurologic or gynecologic origin. Data on the commonest causes of backache are difficult to obtain. Published statistics must be interpreted in the light of the writer's specialty. The internist, orthopedist and gynecologist will differ on "the commonest cause." Kuhns considered trauma, faulty posture and fatigue the most frequent causes. According to Albee myofascitis is the commonest cause; Hartung considered most backaches due, not to one factor, but to a combination of postural, arthritic, traumatic and congenital factors.

*Postural Backache.* Milliken believed that one may "assume the case to be postural if no other pathology is found" on careful examination. According to Brown, in the drooped position of the thorax seen in faulty body mechanics it is possible to get pressure or stretching of the intercostal nerves with radiating pain. This pressure may come from acute or chronic inflammation due to strain of the costovertebral or costotransverse joints. According to Henry, poor abdominal musculature permits increased sacral inclination which, whether it is the cause or result of faulty body mechanics, throws a strain on the lumbosacral ligaments and articulation. According to Hartung, exaggerated lumbar lordosis is the cause of most postural defects. Indiscriminate exercise is valueless; exercises recommended are those which tilt the front of the pelvis up and the back of the pelvis down.

*Sacro-Iliac and Lumbosacral Strain.* Sacro-iliac strain and dislocation as causes of backache have been greatly exaggerated.<sup>241, 305, 370</sup> The pathogenesis, symptomatology and treatment of lumbosacral strain and its differentiation from sacro-iliac strain were reviewed.<sup>374, 375</sup> "Sacrarthrogenetic telalgia" was the formidable term applied by Pitkin and Pheasant to "the typical syndrome of pain which originates in the sacro-iliac and sacrolumbar articulations and their accessory ligaments." Under this heading were given a study of referred pain, sacral mobility, alternating scoliosis, differential diagnosis of "sacrarthrogenetic scoliosis" and treatments used in 1000 cases of low back pain.

*"Post-Operative Backache."* This is most often caused by the inadequate support of lumbosacral muscles in a sagging bed. Berman prevented it "easily" by incorporating a new "movable semicircular spring unit" in regular hospital beds.

*Utrine Displacements.* These often cause backache, according to Dicks: "Backaches above the lower lumbar and sacral regions have no direct relationship with pelvic disease." However, Holt believed pelvic disease was a rare cause of backache. "The backache most frequently associated with kidney conditions is felt in the costo-vertebral angle, particularly over the superior lumbar triangle."<sup>440</sup>

*Myofascitis.* An infectious or toxic inflammation of muscles and tendons of the lower back is one of the commonest causes of low backache according to Albee. Kuhns considered it a rare cause of low back pain. Lumbago represents acute or chronic myofascitis.<sup>150, 151, 241</sup>

Other causes of low back pain and secondary sciatica were discussed: the rôle of congenital anomalies such as spondylolisthesis, lumbosacral transitional vertebrae, posterior displacement of the fifth lumbar vertebrae, and so on<sup>27, 206, 241, 305, 375</sup>; coccygodynia<sup>305</sup>; contracted iliotibial bands and fasciae producing low back pain and sciatica<sup>413, 414</sup>; diseases of intervertebral disks and conditions secondary thereto.<sup>16, 146, 227, 256, 352, 373, 464</sup>

Clinical and radiologic features of *neoplastic diseases* of the spine were given.<sup>186, 210, 305, 459</sup> Fray discussed radiologic differences between infection

and malignancy in cases in which there is a dorsal paravertebral mass. Important radiologic features of malignancy were preservation of articular plates in the presence of collapse of the body, slight or no narrowing of disk spaces in cases of marked collapse, absence of wedging resulting in little or no kyphos, diffuse increase in bone density, and involvement of vertebral appendages. Normal roentgenograms may be obtained in the presence of metastatic foci of malignancy, for the latter are visible in roentgenograms only when large enough to produce a definite contrasting shadow or when marked osteosclerosis occurs about the metastasis.<sup>210</sup> Cases of vertebral involvement in Hodgkin's disease were reported.<sup>459</sup>

*Diseases of Intervertebral Disks.* The muscular, ligamentous, neural and osseous components of the spine are so closely related anatomically and physiologically that no one part lives unto itself alone. In last year's Review we gave a detailed presentation of the "newer anatomy of the spine," the physiology and pathology of intervertebral disks and posterior facets, and diseases secondary thereto. Current reports contain little different; several<sup>227, 289, 464</sup> reviewed the subject. Certain changes in intervertebral disks may be quite unrelated to a patient's complaint and a given backache must not be incautiously ascribed to such changes found in roentgenograms. Many variations in disks do occur but the consensus of opinion seems to be that many disk changes are of little significance.<sup>256</sup> According to Bailey and Taylor herniation of the nucleus pulposus or the disk usually occurs into a vertebral body, rarely results from sudden trauma, is usually a degenerative process from wear and tear, and is seldom of clinical significance. Herniation of a disk in any other direction than into vertebral spongiosum is often related to sudden trauma and may cause pressure on the spinal cord.

Recently narrowed or ruptured disks have been considered the cause of a wide variety of complaints: compression phenomena, sciatica without neurologic changes, and pains and aches of varying severity about the lower back. Sashin's patients with narrowed disks complained mainly of dull aching pains in the lower back, often of sciatica. They usually gave a history of mild injury, a slight fall or sudden twist. They walked guardedly with stiff, often tilted spines, and had lumbosacral and gluteal tenderness. Lateral and oblique radiographic views of the spine revealed the narrowed disk. Sashin's treatment aimed to reestablish normal lumbar lordosis and to support the spine by rest in a plaster bed or jacket. No manipulation was used.

(Four illustrative cases were given. Narrowed disks were present but the evidence seems insufficient for us to conclude that symptoms in these four cases were actually due to the narrowed disks. Detailed results of treatment were not given.—Ed.)

Narrowing of a disk does not necessarily indicate a protruded disk; narrowing may occur from degeneration and fibrosis of the disk without protrusion, and posterior protrusion may occur without narrowing. In-



deed, according to Camp, narrowing of the intervertebral space at the site of a protruded disk occurs in only a small percentage of cases. Therefore ordinary roentgenograms are only suggestive and of limited value in the diagnosis of herniated disk. In Love's series of cases in which operation was performed, protrusion occurred in any region of the spine, especially the lumbar region. Commonest symptom was sciatic pain. The diagnosis was easy in the presence of neurologic findings: motor weakness, sensory loss, signs of a compression-level in the cord. The diagnosis is difficult in the presence of pain only, with no neurologic findings; it then depends on fluoroscopic and roentgenographic examinations of the spinal canal after subarachnoid injections of lipiodol. One should not do this to all patients with obscure back pain. Love advised it only for the following patients: (1) those whose pain follows the distribution of one or more spinal nerve roots for a considerable period of time and who have not been notably relieved by orthodox conservative treatment, (2) those whose cerebrospinal fluid contains more than 40 mg. total protein per 100 c.c. fluid and reacts positively to a test for globulin (Love admitted, however, that protruded disks with compression phenomena do occur in patients with normal or even low values for total protein in spinal fluid), and (3) those who demonstrate a "reversed Queckenstedt test." This is the most important of all criteria for the use of lipiodol intraspinally, and at times, according to Love, gives the only real clue to the cause of the trouble. [The technic and interpretation of the test were given.] The absence of an increase in the manometric reading and an unbearable pain response provides a pathognomonic sign of a mass pressing on caudal roots. If the protruded disk corresponded to the level of the root pain complained of, then and only then was surgical treatment (laminectomy) performed, for disks can herniate without causing pain.

Intervertebral disks may be injured by lumbar puncture, with subsequent production of symptoms (Pease, 1935). Milward and Grout noted five patients operated on under spinal anesthesia, who at varying intervals (immediately, three weeks, five weeks, four months, six months) after operation, complained of severe pain in the back, occasionally in the lower limbs. They could not stand or sit fully erect. Spasm of lumbar muscles and marked tenderness over one or more lumbar vertebrae were present; in one case, with transient urinary retention. Roentgenograms (well illustrated) showed a rapidly progressive lesion; a progressive arthritis localized to one intervertebral joint, loss of joint space, new bone formation between edges of adjacent vertebrae. Milward and Grout favored Pease's explanation: the needle puncture traumatized the annulus fibrosus with rapid (in children) or slow (in adults) escape of the nucleus pulposus and the subsequent development of localized arthritis.

An unusual case of herniation of the intervertebral disk between the sixth and seventh cervical vertebrae complicated by a localized staphylococcal in-

fection and fatal compression of the cord was reported by Dickson. Hadley again described the possible results of degeneration of disks: thinning of disk, closer approximation of vertebral bodies producing (1) a localized kyphos if posterior articulations do not slip past one another, (2) apophyseal subluxation with reduction in the size of the intervertebral foramina and production of radiculitis, or (3) actual bony impingement between the tip of the articular process and the pedicle above, or the lamina, below (all illustrated in the report). Hadley described a new point in the radiologic diagnosis of apophyseal subluxation: distortion of an "S-line."

*General Measures for Low Back Pain.* Measures discussed were the institution of rest, relaxation and support for the spine, the use of proper beds, strapping, heat, massage, belts, corsets, braces (not to be worn too long), proper shoes, exercises to improve body posture and to strengthen abdominal and spinal muscles.<sup>256, 305, 329</sup> Correct treatment presupposes a correct diagnosis, which is not an easy matter, and can be made only after a thorough physical and radiologic examination. Lewin in particular described with diagrams and photographs the various physical signs and tests useful in differentiation of lumbosacral, sacro-iliac and adjacent diseases. In special cases manipulation for low back pain is most useful.<sup>241, 305, 341</sup> The indications, contraindications, technic and after-care of manipulation were given in detail by Lewin.

Epidural injections of procaine seemed of little value to Kimberley. Special indications for facetectomy, fasciotomy, and lumbosacral fusion were given.<sup>206, 328, 370</sup>

#### SCIATICA

Classifications of sciatica were reviewed<sup>38</sup>; Douthwaite used a familiar one: (1) sciatic neuritis, acute or chronic—(with neurologic changes), (2) central sciatica, acute or chronic (as a rule without neurologic changes) often called by others "secondary sciatica" or "sciatic pain." The latter is generally secondary to disturbances in the lumbosacral region. "Real sciatic neuritis" with neurologic changes in sensation and reflexes, and muscle atrophy in thigh or calf are rare, according to Henry, who regarded the commonest form of sciatica to be usually a symptom, not of nerve trunk disease but of hamstring spasm or irritation of the piriformis muscle from arthritis or other cause. Douthwaite wrote of the possibly serious significance of bilateral sciatica. "Any patient with sciatic pain in both legs must be suspected of a central—e.g. vertebral, spinal or pelvic disease, not forgetting the very real possibility of a cauda equina tumor." All other examinations including that of cerebrospinal fluid must be negative before accepting a diagnosis of "simple" bilateral sciatica.

Causalgia (neuralgia characterized by intense, local, burning pain) rarely affects other than the median nerve, the tibial portion of the sciatica, and less often the ulnar nerve. Karnosh reported two cases which supported the view that sciatic causalgia results from ischemia of the nerve trunk.

Ten days after striking his right gluteal region and developing a hematoma, a patient began to complain of paroxysmal burning, dragging pain in a heel, extending into the calf. At exploration it was found that the nutrient artery to the sciatic nerve had been severed. Another patient developed sudden burning paresthesia of a foot while at work. For reasons given a diagnosis of sciatic causalgia from thrombosis of a nutrient artery was made.

*Treatment.* The usual measures of heat and rest were advocated. For "rheumatic sciatica," polyvalent streptococcal vaccine suspended in oil (lipovaccine) was injected by G. L. Scott into perineural tissues and "into the fibrositic areas which seem always to be associated with neuritis of this type"; of 15 patients 12 were rapidly "cured"; two were "benefited"; one was not.

Epidural injections of normal saline through the sacral hiatus seemed to Wallace to be "far the best treatment for chronic sciatica." (No results were given.) Subarachnoid injections of alcohol were used by Goff to relieve "sciatic neuralgia." Although there is some danger of motor depression and paralysis, this rarely results, according to Goff, because motor nerves are myelinated and well protected, offering great resistance to the caustic action of alcohol. Of 20 patients with "intractable pain" so treated 15 were "relieved at once"; the other 5 were "relieved the same day." A few had a return of pain within the first two weeks but at the end of three weeks 18 of 20 were "entirely relieved." Eight had temporary urinary retention.

(We believe that such injections are not without danger except when done by experts; they constitute symptomatic treatment only and should only be done under special circumstances in cases unrelieved otherwise.—Ed.)

Bee venom gave relief in some of Mackenna's cases of "sciatic neuritis." (Very meager details were given.) Taylor-Pergalley recommended "labile diathermy"—one electrode kept in motion over the area treated.

Manipulation may bring dramatic relief in certain cases of secondary or central sciatica.<sup>150, 341</sup> Lewin described indications and methods in detail. Ober gave further results from his treatment of sciatica by incision of contracted iliotibial bands and fasciae. A new skin incision was used. Forty-two patients were treated: 23 were cured, 10 were improved, 9 not improved. A few noted relief "at operation." The majority noted relief of sciatic pain beginning the fifth to the tenth day after operation. "The lame back clears up in from six weeks to six or eight months but occasionally lasts longer." The rationale of the procedure was given: Shortening of the iliotibial band and its fascial expansion causes an abduction contracture of the femur, "resulting in a tremendous leverage action on sacroiliac and lumbosacral joints. Any contracture of the fascia lata must exert muscular pressure on the sciatic nerve which lies beneath the gluteus maximus where it emerges below the piriformis." According to Ober many cases of lumbosacral, sacro-iliac and sciatic pain are so caused. Nutter noted relief

in several cases in which the nerve was explored and iliotibial bands sectioned. The mechanism of relief was uncertain because in some cases tight bands were not found and no irritation of the nerve trunk was seen although relief was obtained. According to Cave "it is the correct diagnosis of iliotibial contracture and not the Ober operation that is difficult." Diagnostic tests were described. Results of fasciotomy in six cases were: two cures, two "fair results," one "poor result," one "failure." Of 32 patients treated by a colleague of Ober, results were "perfect" in 27 per cent, "good" in 34 per cent, poor in 39 per cent.

#### COMMON TYPES OF SPONDYLITIS

Two clinical types were recognized, corresponding to two distinct pathologic types: (1) atrophic spondylitis, (2) hypertrophic spondylitis. "Atrophic spondylitis" is synonymous with "rheumatoid spondylitis," and "spondylitis ankylopoietica" or "ankylosing spondylitis." Most current writers were unwilling to subdivide atrophic spondylitis further and considered the so-called subvarieties (a, spondylitis ossificans ligamentosa or Marie-Strümpell type; b, spondylitis muscularis or von Bechterew type) minor variations of one disease. Hypertrophic spondylitis is synonymous with osteo-arthritis of the spine, spondylitis osteo-arthritica.

Details of the clinical, radiologic and pathologic differences of these two main types (and of the subvarieties of the first type) were given in the second review and have been given again.<sup>203, 269, 505, 535</sup>

Atrophic spondylitis generally appears in men below 40 years of age, exhibits an increased sedimentation rate and other nonspecific signs of an infection, involves sacro-iliacs early, and stiffens the spine chiefly by a process of ligamentous calcification. Hypertrophic spondylitis generally appears after the age of 45 years in either sex, is not associated with the chemistry of infection, does not involve sacro-iliacs early or characteristically (although they may be affected), produces moderate stiffening by formation of osteophytes which only occasionally coalesce to form isolated bridging, not diffuse regions of ankylosis.

Egyptian mummies exhibited only atrophic arthritis according to some (Jones, 1907 and 1908, Smith and Jones), both atrophic and hypertrophic arthritis according to others (Moodie, 1923, Ruffer, 1926). Shore's examination of spines of predynastic Egyptians would indicate that several types of spondylitis were extant, tuberculous, possibly staphylococcal and other definitely microbic types, also atrophic and hypertrophic types. One, perhaps two, of his seven specimens showed ossification of perivertebral fibrous sheath. Specimens of localized and generalized hypertrophic spondylitis were noted.

#### ATROPHIC SPONDYLITIS

Three views were expressed: that atrophic spondylitis (rhizomelique) is (1) identical with atrophic arthritis elsewhere and is merely atrophic arthritis in the spine<sup>505, 535</sup>; (2) a separate disease but "somewhat like," or

"having much in common with," atrophic arthritis<sup>58, 203</sup>; (3) not one disease but a pathologic end result of several diseases.<sup>83, 369</sup> Much like atrophic arthritis elsewhere, according to Buckley and Golding, atrophic spondylitis differs from the former in several particulars: ligamentous calcification extending some distance from joints as seen in spine, rib articulations and hip joints, is not a feature of atrophic arthritis; the age and sex incidence of the two are dissimilar; the spine is involved seldom in atrophic arthritis, and the small joints rarely in spondylitis; remissions are much commoner in spondylitis than in atrophic arthritis. Miller<sup>368</sup> viewed atrophic spondylitis as a pathologic but not a clinical entity. "Ankylosing spondylitis is infective in character and, unlike rheumatoid arthritis of extremities, may be produced by a variety of microorganisms, and develop as a complication of various diseases, such as rheumatoid arthritis, gonorrhea, typhoid fever, bacillary dysentery and influenza; one case has been reported after undulant fever. Without regard to the nature of the infective agent, the pathologic changes are identical." Again he wrote<sup>369</sup> "one must bear in mind that in only a small percentage of cases is spondylitis ankylopoietica due to the infection responsible for rheumatoid arthritis. The gonococcus is responsible in a large percentage of cases." The usual absence of streptococcal agglutinins suggested to Cecil that "spondylitis deformans is not always referable to the streptococcus; this would fit in with our clinical observations, for one sometimes sees this form of arthritis coming on after gonorrhea or even after typhoid fever."

(We cannot accept the view of Miller and Cecil. Admitting that the cause of atrophic spondylitis is unknown, we know of no proved cases of gonorrheal or typhoid spondylitis with the chronic clinical course and pathologic reactions of atrophic (ankylosing) spondylitis. Proved cases of gonorrheal arthritis are not chronic and progressive but practically always acute or subacute in onset and course. Typhoid fever produces a localized spinal abscess with resultant localized hypertrophic reaction. The reported manifestations of undulant fever in the spine have not resembled the clinical or pathologic features of chronic atrophic spondylitis.—Ed.)

A new series of 124 cases (106 males, 18 females) was studied by Golding. The disease was not more common in manual than in the sedentary workers; 73 per cent of these patients led sedentary lives. Many were free of foci of infection. Blood calcium was high normal. Only nine patients gave a history of gonorrhea. In early cases with sacro-iliac changes only, sedimentation rates were generally elevated (5 to 123 mm.) but on the average not as high as in those with sacro-iliac and spinal radiologic changes in which rates were 9 to 110 mm. Golding and Scott repeated Scott's ideas on pathogenesis. All of Scott's 110 cases and of Golding's 124 cases (they may have been overlapping cases as the two writers collaborated) showed radiographic indication of bilateral "infection" of both sacro-iliac joints ("sacro-iliitis") usually with ankylosis. These changes were regarded as long antedating any spinal involvement. According to Scott and Golding the sacro-iliitis generally commences several years before



any symptoms referable to the back or even to the sacro-iliac joints themselves, and has "not therefore been clinically recognized as a manifestation of spondylitis *adolescens*" (Scott's term for the disease). The patient's course is presumably as follows: He develops vague spells or more definite attacks of "wandering pains" across shoulders, down arms, round the ribs, and finally down the thighs, pains of a fibrositic character recurring over several years with free intervals. This is the "pre-spondylitic phase," the pains of which are referred to muscles or near joints and are occasionally associated with a resolving synovitis of peripheral joints. There may be "tightness of chest" and (according to Golding) pains in thighs and buttocks. "Pain in the back or sacro-iliac region is not present at this period."<sup>478</sup> Presumably the patient is insidiously developing sacro-iliitis which is apparently relatively symptomless until the disease is well advanced. It may cease any time and spondylitis never develop, or it may progress. No spinal symptoms (rigidity, pain) are complained of until sacro-iliac ankylosis has already begun. Of Golding's 124 patients, 33 presented sacro-iliitis alone, 91 had spondylitis with advanced sacro-iliitis. Scott therefore regarded the sacro-iliitis the source of the spinal infection: "If this source of infection can be removed or adequately dealt with, spondylitis in the young adult will cease to exist." In three early cases of sacro-iliitis trephining was done: pus was absent, cultures were contaminated, the bone was grossly diseased; the operation "certainly proved beneficial." Scott recommended more conservative therapy—wide field radiation with roentgen-rays of medium length. Results were "so encouraging that the method is being adopted in all cases seen early enough." Several patients so treated were free of symptoms, one for five years.

Weil also held that the fibroid calcification (ligamentous ossification) is a defensive affair secondary to sacro-iliac arthritis and arthritis of the posterior vertebral articulations. It is possible, "by recognizing and treating this arthritis in the early stages, to prevent the development of its subsequent lesions, and to reduce or do away with the painful invalidity resulting from it." Prevention and early recognition, according to Scott, necessitate an early radiographic examination of sacro-iliacs "in every case where recurrent attacks of muscular rheumatism extending over a number of years, occur in the young adult."

(Scott has not yet proved his hypothesis. Even were the sacro-iliitis the "focus of infection" for the spine, which is not proved, what is the source of the sacro-iliac "infection," by what means does it spread to the spine? So far its infectious nature is only a fairly logical presumption. Even were one to discover the early lesion it has not been shown that the therapy of Scott, Weil or any other will consistently check it. Final results of Scott's therapy after five years or more will be awaited with interest. Others have noted early and frequent involvement of sacro-iliacs in atrophic spondylitis but have not considered it the consistent etiologic precursor of spondylitis. In their study of 11 cases of at least two years' duration each, Taylor, Ferguson, Kasabach and Dawson noted calcification of spinal ligaments and ankylosis of intervertebral facets in 100 per cent; the latter was "almost

invariably" (but not invariably) accompanied by sacro-iliac obliteration. Some of us do not recall seeing a case of atrophic spondylitis with radiographically normal sacro-iliacs. Others of us believe that cases of undoubted atrophic spondylitis with radiographically normal sacro-iliacs are occasionally seen. One of us, J. A. K., examined two skeletons with typical spinal ankyloses from atrophic spondylitis in which sacro-iliacs were not involved.—Ed.)

*Pathology.* Miller noted one of the reasons for the unusual pathologic reactions of atrophic spondylitis as compared to atrophic arthritis elsewhere: in the latter situations the disease first involves synovia. Since intervertebral disks do not have synovia, atrophic arthritis cannot reproduce in disks (the big "joints" of the spine) the same pathologic reaction it produces in peripheral joints. However, as the disease attacks the "true joints of the spine" (the facets or articulations of the transverse processes, which possess synovia), the same pathologic reactions are presumably produced here as in peripheral joints. (Studies on the pathologic reactions in the true joints of the spine in spondylitis are needed.—Ed.)

*Treatment.* Scott's treatment was noted. Others advised the usual treatment as for atrophic arthritis elsewhere with certain additions: extra rest in bed on a proper bed in a proper position; breathing and other exercises; plaster shells and braces to prevent and correct deformity. Without giving results, Buckley recommended Ponndorf's vaccine B, roentgen-ray therapy, and gold. Baker considered gold useless. The usual physiotherapeutic methods were advised. Speeding regarded short-wave therapy dubiously. Histamine by injection<sup>157</sup> or by ionization<sup>396</sup> was recommended for analgesia. Stecher's six patients received 19 fever treatments with considerable analgesia but no increased mobility. Improvement had lasted one year in one case, six months in five cases. Hartung recommended paravertebral injections of procaine or alcohol, or epidural injections for root pains which some considered common,<sup>369</sup> others rare.<sup>59</sup>

#### HYPERTROPHIC SPONDYLITIS

A localized hypertrophic spondylitis may be the pathologic or radiologic end-result of several causes: trauma, typhoid, undulant fever, or other infection. In the clinical sense, "hypertrophic arthritis" is an entity synonymous with hypertrophic arthritis elsewhere. We<sup>247</sup> previously gave a detailed account of the relationship between degenerative changes in the intervertebral disks and hypertrophic spondylitis. Miller summarized this relationship developed by Schmorl and others. The disease is the result of primary degenerative and secondary hypertrophic reactions due to the wear and tear of traction and trauma.<sup>58, 369</sup>

Considerable attention is being paid to its neurologic manifestations. Some<sup>369</sup> are "very positive" that root pains are not directly due to osteophytes. However, the generally accepted cause of root pains is that nerve roots are pressed on by osteophytes in the spinal canal or at the point of emergence from the foramina.<sup>59</sup> Such a radiculitis was present in 30 cases

of cervical hypertrophic arthritis reported by Hanflig. Pain and other sensory, and sometimes motor, disturbances were produced most often about the shoulder girdle, less commonly at the back or side of the neck and down the arm, occasionally in the precordial region. Hanflig's patients complained of pain of variable severity, sometimes "agonizing," sometimes numbness and weakness of hand, muscle incoördination, at times some muscle atrophy, loss of position sense, even absent reflexes and flaccid paralysis. Varying degrees of muscle spasm and cervical rigidity were noted and rotation of the neck often sharply accentuated the complaints. The cases were frequently misdiagnosed arthritis of shoulder, bursitis, toxic neuritis. In every case cervical hypertrophic arthritis was present and shoulder joints were negative. In each case nerve symptoms corresponded to the cervical segment involved with osteophytes.

The variability and type of pain can be understood from the following: The fourth cervical segment supplies the sensory innervation over the top of the shoulder; the fifth supplies the sensory innervation of the outer surface of the arm between the shoulder and elbow. The deltoid muscle is supplied by nerve fibers derived from the fifth and sixth cervical segments. The pectoralis major and minor are innervated by the medial anterior thoracic nerves (which come from the eighth cervical and first thoracic spinal segments) and the lateral anterior thoracic nerve (from the sixth and seventh cervical segments). Although the latter two are motor nerves and do not carry skin sensory fibers, they can possess protopathic sensations, so that irritation of them may produce diffuse yet definite pain referred to the terminal portion of the nerve. When the anterior roots of spinal nerves are sufficiently involved, there may even be muscle incoördination, loss of position sense, absent reflexes or flaccid paralysis.

The same symptoms which Hanflig noted in cervical hypertrophic arthritis were noted by Turner and Oppenheimer in 50 cases with narrowed cervical intervertebral disks (the precursor of hypertrophic changes) whether cervical hypertrophic arthritis was present or not. Chief complaints were pain in some part of the shoulder girdle, neck, arm, hand, back or precordium; occasionally weakness or inability to perform certain movements (writing, combing hair, fastening buttons, grasping or steering automobile wheel, elevating hand above head "as in the Fascist salute"). Some complained of tingling fingers, pain on turning neck, or on walking or riding; sometimes inability to sleep because of pain in the recumbent position. Others complained of precordial pain—"angina" or "aortitis." Unlike Hanflig's patients (with later pathologic changes), these patients generally had no pain in the neck or definite limitation of neck motion; their commonest complaint was unilateral shoulder pain. Atrophy of small muscles of the hand was sometimes noted. Neurologic symptoms invariably coincided with the cervical region involved in the narrowed disk, with or without hypertrophic arthritis. Oblique radiographic views (illustrated) showed actual narrowing of intervertebral foramina even when narrowed disks were present without hypertrophic arthritis.

Because of these experiences, Hanflig, and Turner and Oppenheimer rec-

ommended special clinical and radiographic examination of cervical spines in cases of unexplained shoulder and arm pains and of "angina" without evidence of cardiac disease. Although osteophytic changes are commonly seen on the anterior and lateral aspects of cervical vertebrae they are rarely found on the posterior aspect. Morton demonstrated the latter in three cases which showed that hypertrophic processes can develop posteriorly, and whether posterior or lateral, can extend into the spinal canal and press on the cord, or encroach on the cervical foramina and cause symptoms. Morton demonstrated the posterior projections clearly in oblique roentgenograms. Two of his three patients had pains in one or both arms, hand and neck. One had numbness and tingling of extremities, uncertainty in walking and girdle sensations accentuated by cervical hyperextension. A subarachnoid block was present. The projection was found at laminectomy, after which the patient was "considerably improved."

*Treatment.* Treatment used in Hanflig's cases included a special type of stretching and manipulation. The patient was gently and carefully "hung" by his neck supported in a Sayre's sling suspension with block and tackle. Suspension was repeated for a few seconds each session and two or three sessions were given daily, usually only for a few days. At times, hot fomentations were given and a Thomas collar was worn between sessions. Results were often dramatic, severe pain disappearing immediately while the patient was suspended, returning thereafter but rather rapidly disappearing under continued treatment, usually within 10 to 21 days. Turner and Oppenheimer also noted marked relief with this method which was much easier than manual traction. Ultra short-wave therapy relieved a few, as did soft rubber soles and heels in mild cases. For usual cases of hypertrophic spondylitis short-wave therapy seemed valueless to Speeding. Gold was useless.<sup>18</sup> Histamine ionization reputedly gave analgesia.<sup>396</sup>

#### GOUT AND GOUTY ARTHRITIS

Gout was called a "forgotten disease."<sup>261</sup> Current statistics on its incidence foster contradictions: that it is rare or that it is fairly common. Pringle found the incidence rising in some English and continental hospitals, falling in others. At the Philadelphia General Hospital a diagnosis of gout was made on only 47 of 414,296 patients admitted in 25 years (1905 to 1929), an average of less than two cases a year, but between 1929 and 1935 it was made on 30 of 146,992 patients.<sup>91</sup> Cohen saw 40 cases the past 5 years. According to Schnitker, only 55 cases of "true gout" were admitted to the Peter Bent Brigham Hospital, Boston, between 1913 and 1935. Only five cases of gout were seen at the arthritis clinic of the Presbyterian Hospital, New York, in 1935; in the same period Herrick and Tyson saw six cases in private practice. Such statistics do not give an accurate index of the situation because the requirements of different physicians for a diagnosis of gout differ so materially. Hench stated that only one of

four or five cases of gout is correctly diagnosed in its early stages. But in some quarters, where physicians are loose with a diagnosis of gout, only one of two or three patients who receive such a diagnosis actually had the disease. In Hench's 100 cases of gout an average of 15 years had elapsed from the first attack of gouty arthritis to the first diagnosis of gout. "The necessity of taking 1500 years to diagnose 100 cases of classical gout does not indicate a proper understanding of this disease."

The features of classical gout were reviewed by several (Cohen, Hench, Herrick, and Tyson, Kersley, Pringle). In diagrammatic fashion, Hench described the basic pattern of gouty arthritis in relation to the appearing time of the four reported features of gout (podagra, hyperuricemia, tophi, punched-out areas in roentgenograms). He divided the course of gouty arthritis into two stages, each consisting of two phases: Stage I is that of acute, recurrent gouty arthritis with complete remissions (phase 1 is that of early attacks; phase 2 that of later, acute attacks with remissions and when hyperuricemia is more established and discoverable). Stage I lasts 3 to 42 (av. 12) years. Stage II is that of chronic gouty arthritis (phase 3 is that of early chronic gouty arthritis with acute exacerbations but incomplete remissions; phase 4 the final, relatively symptomless, chronic gouty arthritis).

Discussing criteria for diagnosis of gout Hench noted 20 points expressed axiomatically.

These were: Suspect gout when acute arthritis suddenly develops (1) after relatively trivial trauma; (2) after dietary excesses of holidays, birthdays, lodge-night; (3) after any surgical operation ("Acute postoperative arthritis is generally gouty"); (4) after the trauma, exposure and dietary insults of a fishing or hunting trip; (5) in spring or fall (gout has a definite seasonal incidence); (6) in the night between 2 and 7 a.m. (it may occur any hour, however); (7) in patients under certain coincidental treatments such as liver diet for pernicious anemia, ketogenic diet for bacilluria, salyrgan for dropsy, ergotamine tartrate (gynergen) for migraine, insulin for diabetes; (8) acute arthritis occurring in patients with polycythemia or leukemia is usually gouty; (9) to diagnose gout in females requires extra caution: 98 per cent of provable gout is in males; (10) gout is the commonest form of acute arthritis in men over 40 years; it may occur in youth; (11) suspect gout when acute arthritis comes on with dramatic speed, within a few minutes or hours; (12) when the pain is unusually severe, "the worst ever"; (13) when the great toe is acutely, not chronically, involved; however, podagra may occur late or never in the disease; (14) when the maximal tenderness is at the mesial aspect rather than underneath or on top of the "bunion joint"; (15) the appearance of an involved foot is suggestive (warm, bluish-red rather than cold and bluish-white as in atrophic arthritis), with edema and later desquamation of skin; (16) an acute arthritis of short duration (one to three) weeks and with full restitution of function should make one suspect gout; (17) any case with acute recurrent attacks of arthritis and complete remissions, possibly chronic arthritis later, should invite a diagnosis of gout; (18) since olecranon bursitis is several times commoner in gout than in any other disease, suspect gout in patients who have or give a (sought-for) history thereof; (19) suspect gout in patients with acute or chronic arthritis who have or have had chronic nephritis or renal colic (urate stones or gravel which incidentally cast no roentgenographic



shadow); (20) podagra is a common but not inevitable feature; hyperuricemia, "characteristic" roentgenographic changes, and tophi are not early but rather late features of gout. Therefore in a case presenting a number of the features listed above one must not hesitate to entertain a diagnosis of gout in the absence of the four most characteristic features.

Some of these points were stressed by others also. Campbell noted the potency of trivial trauma as a provocative. Many stressed, but others minimized, the provocative nature of dietary excesses. One of Cohen's patients developed an attack after alveolectomy, another attack two days after appendectomy. Another patient noted an attack after tonsillectomy. Two of Herrick and Tyson's six patients were women who were taking liver extract orally, one for "a skin condition," the other for an unstated reason. Burchell reported a case of pernicious anemia with uric acid deposits in renal collecting tubules. No history of gouty arthritis was given; the patient suddenly died some time after stopping the use of liver extract in favor of ventriculin. Herrick and Tyson stressed the diagnostic importance of (1) the pattern of gouty arthritis, its recurrence with complete remissions, (2) a therapeutic test with colchicine. According to Graves (1863) gouty patients tend to grind their teeth and produce "bevelled teeth." "Graves' sign" was mentioned by Pringle, Finkle and Kersley; the last considered it by no means diagnostic and not always present. "Coates' sign," defined by Kersley as radial, by Pringle as ulnar, deviation of the terminal phalanx of the little finger, was mentioned. (One of us, P. S. H., has not noted Graves' or Coates' sign as a feature of gout in a study of several hundred cases of tophaceous and pretophaceous gout.—Ed.)

Clinical features of 84 cases were recorded by Cohen: There was a notable incidence among Philadelphia policemen and firemen. Eapen noted chronic advanced tophaceous gout in a Chinese male. Kendall, Fortner and Livingston noted a patient with a painful stump, the leg having been amputated for epithelioma. Later the stump became too painful for an artificial limb to be worn. From the stump a small nodule was excised; it contained scar tissue and giant cells. Within the cells, but not elsewhere, were "uric acid crystals." A diagnosis of gout was made thereon and also because the blood uric acid was 7.2 mg. per 100 c.c. and the "usual medical treatment" for gout was followed by relief of symptoms.

(This case may have been one of gout. However, it is difficult for the reader to accept such a diagnosis without reservations. Crystals were identified only on their appearance, no murexide test was mentioned. There was no history of acute arthritis or other feature of gout. The presence of the crystals only within giant cells is an unusual feature, possibly due, as stated, to their destruction by the fixative used. The case is interesting and unique.—Ed.)

Of the 55 patients studied by Schnitker and Richter, 17 (31 per cent) had clinical nephritis, of the vascular type in 15, and of the glomerular in two (one with nephrosis). Five died in uremia; four were examined post-mortem, three had vascular, one had glomerular, nephritis. Of the 38 pa-

tients without definite nephritis, 16 had albuminuria with little or no renal insufficiency. Compared to control groups, the incidence of hypertension in the 55 cases of gout was high (54 per cent), as was also that of vascular disease (67 per cent). According to Burchell, uric acid is occasionally deposited as free acid in renal tubules of the newborn (uric acid infarcts), or of leukemic adults; it is much more rarely deposited as urates, not free uric acid, in renal interstitial tissue in gout. Thus, interstitial deposition suggests gout, tubular deposition merely suggests hyperuricemia. In gout with leukemia, uric acid is deposited in tubules, urates in interstitial tissue. No renal deposits were mentioned by Schnitker and Richter.

(We understand that a formalin fixative was used. Many valuable specimens of kidneys and joints are spoiled for complete pathologic studies because of this error. Formalin-containing fixatives promptly dissolve urates. Galantha's (1935) method, using absolute alcohol as a fixative, is recommended.—Ed.)

*Atypical Gout.* Kersley accepted the following features of "atypical or covert gout": an articular history very similar to that of atrophic arthritis, supported by a familial history of gout, by Graves' or Coates' sign, perhaps by podagra, hyperuricemia, and radiographic alterations. It is "distinguished with difficulty from the type of rheumatoid arthritis occurring at the climacteric and from certain cases of focal arthritis." Pringle also suggested that perhaps many cases of climacteric arthritis, Heberden's nodes, fibrositis and panniculitis are atypical gout. (We cannot agree.—Ed.) Manifestations of the latter, according to Cmunt, include dry eczema and hyperkeratosis of skin and nails, and pretibial edema ("due to irritation of periosteum") frequently seen in patients with hyperuricemia but no arthritis.

(We have seen many cases of tophaceous gout, always with the classical pattern of gouty arthritis; acute attacks, complete remissions, and we practically never have seen or heard of cases of atypical gout which went on to formation of demonstrable tophi. It is impossible for us, therefore, to accept a diagnosis of atypical gout in cases of arthritis chronic from onset.—Ed.)

Wood presented four cases of "inflammatory disease in the eye due to gout." The patients had episcleritis periodica fugax. No gouty arthritis or other features of classical gout were present but the patients ate and drank to excess and in two of them the blood uric acid was "greatly increased" (4.6 and 4.1 mg.) during the episcleritis and fell later (to 3.5 and 2.3 mg.). In one case the disease responded to dietary restrictions. Tiny brown crystals "the size of average bacteria" were noted once in the cornea, and once in the posterior sclerotic. These were assumed to be urates; no chemical identification was possible as they were discovered in fixed specimens.

(The diagnosis of gouty episcleritis remains quite unproved. The illustrated "crystals" do not resemble urates. The therapeutic test was unconvincing. The pathologic reaction noted in the one specimen examined included none of the char-

acteristics of gout (giant cells, and so forth) of other tissues. We are very skeptical about the existence of atypical gout. To our knowledge tophi, the one infallible sign of gout, are practically always absent in such cases. In those very rare cases where tophi are present without arthritis (as yet), one still cannot blame every coincidental disease on gout. In a considerable experience with tophaceous gout we have not seen episcleritis or dermatitis as a feature.—Ed.)

*Laboratory Data.* It was generally agreed that hyperuricemia is usually, but not always, present in classical gout, and alone is of limited diagnostic value.<sup>91, 251, 261, 303, 443</sup> The sedimentation rate is occasionally elevated.<sup>87, 303</sup> Roentgenograms are generally negative in early cases and are of no help in diagnosis until late in the disease.<sup>251, 261, 443</sup> Radiographic features in 12 cases were reported without clinical details.<sup>535</sup> Regardless of what joints may be affected, Scott and Kersley recommended roentgenograms of hands—they may show characteristic changes not seen elsewhere.

(In the experience of one of us, P. S. H., roentgenograms of feet show the characteristic signs earlier than those of hands. In the absence of other data a diagnosis of gout based on the presence of punched-out areas with chronic arthritis is usually erroneous.—Ed.)

*Pathology.* The articular pathology was briefly reviewed by Jordan.

*Etiology and Pathogenesis.* Nothing new was presented. Cmunt approved the allergic theory and stated that certain purines seem harmless, but occasionally a purine-free diet, containing a food to which a patient is sensitive, may provoke gout. An 18 year old girl with a serum uric acid of 12 mg. developed a "typical gouty attack" after eating a sour gherkin. The aromatic admixture of wine and not its alcoholic content may be harmful according to Cmunt. Uric acid acts as an allergen only in certain cases.

Tophaceous gout with extensive urate deposits on extremities and in joints was produced by Bollman and Schlotthauer in turkeys on a diet of turkey mash plus urea or raw horse flesh but not in those on turkey mash alone or with certain other additions.

*Treatment.* His report on a "history of the treatment of gout" might as well have been titled a "demonstration of the slow progress of medicine," according to Schnitker. About the only things we don't do that the ancients did are "cupping, fancy poultices and pewking." It is particularly unfortunate that gout is so often unrecognized because, as Herrick and Tyson stated, of all the arthritides gouty arthritis can be most readily controlled. Cohen considered treatment highly successful: "gout is controllable." The usual therapy was reviewed by several: for the attack, rest in bed, protection for joints, hot compresses, purgation, colchicum, cinchophen or salicylates and alkalies, a diet high in carbohydrates and nonpurine containing proteins, low in fats and free of purines.<sup>91, 222, 261, 297, 303</sup> It is important to continue certain measures indefinitely after the attack is over. "Interval-treatment" includes purine restrictions, avoidance of alcohol and traumatizing activity, and the intermittent use of certain drugs.

During an attack Herrick and Tyson prescribed colchicine, 1 mg. q.i.d. the first day; t.i.d. thereafter until symptoms subsided or diarrhea occurred. Cohen prescribed colchicine 1/120 grain t.i.d.; Kersley used the tincture, 15 minims every three to six hours, with alkali and phenacetin or pyramidon. After the attack, Kersley prescribed cinchophen 7.5 grains t.i.d. three consecutive days a week for three to four weeks, thereafter once a day three days a week, "with plenty of carbohydrates and calcium." Neocinchophen was used by Herrick and Tyson only for one week after an attack. Cohen's interval-treatment was a purine-low diet and colchicine 1/120 grain t.i.d. one out of every four weeks.

(Cohen admitted that this did not lower the blood uric acid and it would appear that his patients so treated were usually "on the edge" of a gout attack. The pharmacologic effects of colchicine and cinchophen are quite different. Aside from the question of cinchophen toxicity there is no reason why both should not be used during an attack. There seems to be little rationale for continuing colchicine indefinitely; its value is chiefly analgesic, secondarily purgative. For those who are unable to control their gout by diet alone, the intermittent use of cinchophen seems more rational to some of us, but not to W. B., than that of colchicine, which does not affect urate excretion.—Ed.)

Histamine injections were used by some; no results were stated.<sup>157, 481</sup> "There is probably no disorder so ill-adapted to the injudicious employment of physical methods as [acute] goutiness" (Ray). In intervals between attacks, spa therapy may be of value; however, it may initiate an attack if one is impending (Kersley).

*Cinchophen Toxicity.* No case of cinchophen toxicity in gouty patients was reported. A patient with chronic polyarthritis (type not stated) developed nonfatal subacute yellow atrophy of the liver after taking oxyliodide 0.2 gm. q.i.d. for eight days.<sup>143</sup> Another patient<sup>483</sup> had gonorrheal arthritis; he developed nonfatal agranulocytosis without jaundice or hepatitis after taking cinchophen 0.5 gm. t.i.d. for about three weeks. Palmer and Woodall reviewed all reported cases of cinchophen toxicity. In 141 (73 per cent) of the 191 cases cinchophen had been taken for "rheumatic diseases" ("arthritis" 70 cases, "rheumatism" 52, sciatica eight, gout six, lumbago four, rheumatic fever one). Of the 191 patients, 88 (46 per cent) died. The actual incidence of fatal and nonfatal cinchophen toxicity is probably much greater than reports would indicate. The vast majority of patients are able to take cinchophen over long periods without injury, but a peculiar susceptibility to it may cause disease or death from large or even small doses. Cinchophen had long been used by some without apparent harm, then jaundice and sudden death occurred. In some cases very small doses were used and withdrawn at the first sign of toxicity, yet death ensued. Palmer and Woodall concluded that there was no safe dosage or method of administration of cinchophen. They doubted the wisdom of its use even in gout which can often be handled "satisfactorily over a period of years without cinchophen." Comfort believed its use was justified in gout since there is no pharmacologic substitute for it in gout, but it should not be used otherwise. Its dangers can be reduced by discontinuing its use permanently not temporarily, at the first sign of toxicity and by strictly avoiding surgical

procedures on those so affected, otherwise death may result. Cinchophen being "the drug par excellence for gout" (and for certain other patients with arthritis or lumbago "who were living a miserable existence without it") Westfall considered the slight risk worth taking. Of his miscellaneous patients 1589 each had taken from a few up to 4000 tablets (each tablet 0.5 gm.). Between 25 and 100 tablets were taken by 886 patients, 250 to 500 tablets by 195, 500 to 1000 tablets by 47, 1000 to 1500 tablets by 11, more than this by 8 or 10, less than 25 tablets by the rest. Several took the drug daily for three to four years. Only one death occurred: a woman with cholecystitis developed acute yellow atrophy. Two others recovered from toxic jaundice; mild gastric symptoms were noted in 89 cases, a rash in eight, hives in five. The great majority noted no symptoms whatever. Westfall recommended that the full daily dose be given at one time, after supper, with a "teaspoonful of soda." It should never be given to a patient with liver damage, gastric distress or one on a restricted carbohydrate diet.

In 1933 Barbour and Fisk produced liver damage in rats by large doses of cinchophen. Recently Barbour, with Gilman was unable to repeat his previous work. With large doses of cinchophen and tolysin they were unable to produce hepatic lesions in rats even after attempts to make the liver more susceptible to cinchophen by starvation diets to deplete liver glycogen or by large doses of fat or alcohol. The growth of rats was unaffected by large doses of tolysin but was affected by cinchophen. The antipyretic effect of tolysin appears early and is short, that of pyramidon is delayed but lasts longer. A combination of the two produces a rapid, prolonged effect with no added toxicity.

Unable to produce liver damage in rabbits or rats from cinchophen alone, Radwin and Lederer noted that cinchophen, in combination with intravenous injections of colon bacilli or streptococci, produced no hepatic lesion not produced by infection alone. Sensitivity of patients to cinchophen is therefore a peculiar one not apparently related to previous or coincident hepatic infection. Peptic ulcers and gastric hypersecretion, but no hepatic or other lesions were produced in dogs given cinchophen by Stalker, Bollman and Mann. Reid and Ivy also produced gastroduodenal ulcers but no hepatitis in 100 per cent of 15 dogs. The administration of gastric mucin markedly prevented such lesions and acute toxicity in 82 per cent of 13 dogs.

Hench (1933 et seq.) and others reported that jaundice from cinchophen, and other types of jaundice, produced a marked reduction in symptoms of patients with atrophic arthritis or primary fibrositis. In Diack's case of polyarthritis with hepatitis and jaundice from oxyliodide the condition of joints during jaundice was not described; it was noted that five months later "arthritic pains still persist to a slight degree." The phenomenon described by Hench is apparently relatively specific for atrophic arthritis and primary fibrositis. Others have described certain types of arthralgia or arthritis coming on after, or even with, hepatitis and jaundice. Sager saw a young



woman with "grippe" followed by febrile polyarthralgia (no swelling). About two months later, without the use of cinchophen, jaundice developed; icterus index 100, bilirubin 7 mg. per cent. "With the deepening of the jaundice the severity of the arthralgias had diminished although they never disappeared entirely." Of 208 patients with parenchymatous liver degeneration seen at the Mount Sinai Hospital since 1929, Sager found that 30 (14 per cent) had had "arthritis" or severe arthralgia, of whom 10 had had cinchophen but 20 had not. Cinchophen has been used with great caution since 1932 but Sager's statistics showed that the frequency of arthritis and jaundice did not decrease after 1932. He concluded that certain patients with "arthritis" will develop catarrhal jaundice whether they take cinchophen or not and cinchophen is too often incorrectly blamed for this jaundice.

(In view of the phenomenon noted by Hench and current attempts to reproduce it therapeutically in atrophic arthritis, a more detailed review of these cases by Sager would be of considerable interest. Sager made no attempt to classify arthritis or arthralgias and did not give any time or symptomatic relationships between jaundice and joint disease. Sager called his case of febrile polyarthralgia without swelling "infectious arthritis"; it was probably not atrophic arthritis.—Ed.)

*Uric Acid Problem.* Studying uric acid clearance tests on two nongouty patients McLester concluded that the renal excretion of uric acid is of the same type as that of urea rather than of the type of creatinine and the non-metabolized sugars. Larson and Chaikoff (1935) showed that injections of insulin or of epinephrine increase the blood and urinary uric acid in Dalmation dogs, the urinary allantoin in other dogs. Larson and Brewer have now shown that insulin affects purine metabolism, not per se but indirectly through epinephrine; insulin hypoglycemia produces an increased secretion of epinephrine from the adrenals.

#### PSORIATIC ARTHRITIS: ARTHROPATHICA PSORIATICA

Psoriasis is common and is frequently seen in patients with all manner of articular complaints. Under the term "psoriatic arthritis," writers have listed cases of psoriasis with rheumatic fever, with atrophic arthritis or with hypertrophic arthritis. The reaction to such an indiscriminate application of the term to such cases, the great majority of which have merely been of psoriasis occurring coincidentally with unrelated joint disease, has been that most rheumatologists refuse to believe there is such an entity. A current example of loose usage follows: "Occasionally in the aged, pain and swelling in the larger joints accompany the [psoriatic] rash. This is the so-called psoriasis arthropathica."<sup>152</sup> Others have used certain clinical and roentgenologic criteria to restrict the term to a special syndrome. The matter was discussed by Shlionsky and Blake, who reported a case of what they believed to be true psoriatic arthritis.

A female aged 57 years had suffered with progressive psoriasis and polyarthritis, both of which began 20 years before. Psoriasis was generalized, with coalescent

lesions; nails were thickened, crusted, grooved. Multiple joints, especially those of distal extremities, were involved in a destructive process, with ankylosis in a few joints but with massive bone absorption and the development of "opera glass fingers and toes" ("main en lorgnette") from a veritable dissolution and telescoping of certain joints of wrists, fingers and toes. The patient's serum contained no agglutinins for hemolytic streptococci. The objective and radiographic appearance of the joints was described in detail. Besides osteoporosis and destructive changes, the radiographic feature was a tapered narrowing of articular ends of bones with the production of "ball and socket joints."

(One of us, P. S. H., has called these "pencil-to-pencil joints" or "pencil-in-cup joints" because the end of one bone is destroyed to resemble not a ball but a dull pencil which may oppose a similarly destroyed bone-end or one presenting the shape of a cup.—Ed.)

Shlionsky and Blake considered it a most extensive case of psoriatic arthritis, simulated by only one reported case (Bauer and Vogl, 1931). They believed that the psoriasis and arthritis were etiologically related but were uncertain whether this type of arthritis is peculiar to psoriasis.

(We are divided in our opinion on the specificity of this entity. Some of us (W. B., F. H.) believe that psoriatic arthritis is merely atrophic arthritis and associated psoriasis, this being such a case, and that similar extensive destruction of joints may occur without psoriasis in cases of atrophic arthritis. Others of us (P. S. H., C. H. S.) regard psoriatic arthritis as an entity, a disease which objectively affects central and less peripheral joints, much as in atrophic arthritis, but which has certain pathognomonic features, chief of which is the proclivity with which it affects the distal joints of fingers and toes in a destructive arthritis in conjunction with psoriasis of nails.<sup>247</sup> Although psoriatic arthritis is often fairly mild, it may be severe. Hench has seen in severe cases only, the peculiar type of bone destruction and dissolution noted in this case, an appearance which he has never seen exactly duplicated, even in the most severe cases of atrophic arthritis.—Ed.)

Ingram noted the "association of rheumatic manifestations [of unstated type] in muscles, nerves and joints" in three of twelve cases of pustular plus "ordinary" psoriasis, but in none of 20 cases of pustular psoriasis without ordinary psoriasis. According to Duckworth, nails are not usually affected in cases of pustular psoriasis.

(In scaly, disseminated or patchy psoriasis, nails are commonly involved and sometimes with them the terminal phalangeal joints.—Ed.)

**Treatment.** Most reports on the treatment of psoriasis did not mention joint lesions. Some believe that psoriatic arthritis in its early stages can be largely controlled by vigorous therapy to control the psoriasis. If this is true, treatment of the skin is an important feature of the therapy of psoriatic arthritis. In line with the beneficial effect of summer sunshine on psoriasis, striking improvement in three cases of "notoriously stubborn psoriasis" was noted by Krafka from the use of "massive" (20,000 units daily), later "maintenance" (4000 units daily) doses of vitamin D (haliver oil with viosterol). Small doses were useless. The largest dose was first given in 10 day courses with 10 day rest periods. When the psoriasis had

cleared, the smaller doses were used. Thurmon noted "a decided beneficial effect" from the use of a noncolloidal organic sulfur solution in 70 cases of psoriasis. Colloidal manganese was recommended by Spitz, "psorimangan" by Schwartz. The histopathology of the skin lesions was described,<sup>304</sup> and a historical review of psoriasis was published.<sup>32</sup> Joints were not mentioned in the five papers last mentioned.

### HEMOPHILIC ARTHRITIS

Of 98 patients with hemophilia seen by Thomas, 79 per cent (77 cases) had hemophilic arthritis, 61 per cent (60 cases) had permanent joint deformity. Joints most commonly affected were knees (68 per cent), ankle (56 per cent), elbow (53 per cent), hip (16 per cent), fingers (15 per cent), wrist (5 per cent), spine (3 per cent), toes (2 per cent). Shoulders generally escaped involvement. One case of spinal involvement had been misdiagnosed Pott's disease. One patient had a Volkmann's contracture after extensive hemorrhages in an arm. The patients' ages ranged from the newborn to 65 years. Additional cases of hemophilic arthritis were reported: 11 by Timperley, Naish and Clark, one by Sutton. Firor and Woodhall saw an unusual case of a large, hemophilic, pseudotumor of a thumb with destruction of both phalanges and metacarpals. Previously diagnosed bone sarcoma, the unique lesion represented the end stage of traumatic hemophilic hemarthrosis. "The march of events in small bones has never been ascertained roentgenographically." The pathologic results were similar to those which occur in large bones or joints, but instead of regression and eventual ankylosis, progressive destruction and cutaneous rupture may also occur in small bones and joints.

Crandall found reported four doubtful but no certain cases of hemophilia in negroes. Crandall cited "apparently the first instance" of hemophilia and arthritis in a full-blooded negro. Only five cases of Volkmann's contracture in hemophiliacs have been reported; two new cases were seen.<sup>263, 542</sup>

Roentgenographic and pathologic features<sup>245-247</sup> of hemophilic arthritis were briefly reviewed.<sup>176</sup>

*Treatment.* For joints: This was reviewed by Thomas. Injury to joints must be avoided. Affected joints must be put at rest. In the acute stage, ice bags may lessen pain, reduce swelling, and shorten invalidism. Adequate arterial pressure distal to large hematomas must be insured by blood transfusions if necessary. When contractures have occurred, treatment consists of very slow traction, careful diathermy, gentle massage, carefully applied casts and turnbuckles followed by slow, cautious motion. This may require months during which joints are rested in bed; later, casts, crutches and canes. Firor and Woodhall amputated the thumb affected by the hemophilic pseudotumor safely and rapidly by electrocautery. Normal healing resulted; a remarkable and rather prolonged postoperative reduction

of clotting time from five hours to five minutes occurred, perhaps from some mobilization of thromboplastic substance incident to cauterization.

For the hemophilia: Having used various ovarian substances, corpus luteum, whole ovary, and so forth, with little effect, De Silva controlled hemorrhages of hemophiliacs and others with theelin.

(Data on the cases reported were too meager for one to accept the diagnosis of hemophilia or to approve the conclusion.—Ed.)

A placental extract markedly reduced the clotting time in 11 of 15 cases seen by Eley and associates. Oral use was more effective than intramuscular use. Timperley, Naish and Clark had "excellent results" from a new mixture of potassium bromide and egg white given intramuscularly or intravenously. It did not produce local or general intravascular clotting but reduced the clotting time of blood and controlled hemorrhage of 13 patients so effectively that they endured with impunity such unusual trauma as pounding with a hammer, jumping from chairs, kicking a football, running over uneven ground, dental extraction, and so on. In testing the method "patients were encouraged not to spare themselves the knocks and cuts which of habit they had avoided." Russell's viper venom, applied locally, controlled dental hemorrhages.<sup>20, 73</sup> In Sutton's case of hemophilic arthritis and epistaxis, the venom used locally and orally was ineffective. Injections of whole parental blood and coagulin were helpful.

Of interest was a study of blood coagulation in hemophilia by Patek and Stetson. (In evaluating therapy it should be remembered that the clotting time of hemophiliacs may vary markedly from day to day or from week to week.—Ed.)

#### ALLERGIC, METABOLIC AND ENDOCRINE ARTHRITIS

Though still used by some, these terms are being employed with more caution; they have not yet been accurately defined. Some use the terms to indicate an arthritis presumably different from any other; others consider them more or less synonymous with either atrophic or hypertrophic arthritis. Thus, Pringle wrote, "Though there is not sufficient laboratory or clinical evidence to show that rheumatoid arthritis is a definite disease due to errors in metabolism, clinically I believe that the primary form is metabolic and probably due to some imbalance in the endocrines." Nissen believes that "psychogenic (endocrinal and metabolic) factors" underlie many obscure cases of arthritis. Wootton expressed the belief that arthritis represents food allergy or bacterial allergy in the presence of hyperparathyroidism. "Practically all non-septic joint disturbances begin as an allergic reaction" to bacterial allergens in early life, to food allergens later. But bone changes will not take place unless there is a concomitant hyperparathyroidism.

(This is pure speculation; no proof of any sort was offered.—Ed.)

*Allergic Arthritis.* The application of the allergic hypothesis to rheumatic fever, atrophic arthritis and gout has been noted. No one has been

able to set up any one articular syndrome as "allergic arthritis" or to prove that any of the arthritides are chiefly or solely the result of bacterial or food allergy. Young noted that patients with atrophic arthritis are susceptible to skin allergy but not especially to hay fever or asthma. But patients with such allergy rarely had arthritis. He believed that atrophic arthritis might represent a bacterial allergy but concluded from skin and diet tests that food allergy played no rôle. Some rheumatism specialists consider intermittent hydrops the nearest approach (aside from serum sickness) to an "allergic arthritis." Supporting this view, Lewin and Taub presented a case of "allergic synovitis due to ingestion of English walnuts."

A boy, aged 16, had intermittent (every two to three months) stiffness and swelling of knees for 10 years, attacks lasting 24 hours. His parents had hay fever, and urticaria from strawberries and tomatoes; he did not. A typical attack in knees was induced within 72 hours of eating the meats of half a pound of English walnuts. Skin tests were positive to English walnuts only. Subsequent provocative and therapeutic tests were positive.

"*Metabolic Arthritis.*" Aside from applying this term obliquely to atrophic or hypertrophic arthritis and more directly to gout, current writers failed to stress, or clarify it further.

*Endocrine Arthritis.* The idea that endocrine disturbances may act as predisposing or aggravating factors in atrophic or hypertrophic arthritis is admitted by many rheumatologists and emphasized by a few. But this is a different matter from saying that a certain type of arthritis is due solely to the overfunction or underfunctioning of one particular endocrine gland, in which case a true endocrine arthritis would exist (and not, for example, an infectious arthritis modified by endocrine factors). Ellman and O'Brien accepted a relationship between hypertrophic arthritis and "endocrine imbalance," presumably an ovarian deficiency with or without hypothyroidism or frank myxedema. "A lowered basal metabolism . . . occurs in a noticeably large number of these patients."

(But for hypertrophic arthritis to be a true endocrine arthritis due to hypothyroidism, a lowered rate must *always* be present, which it certainly is not.—Ed.)

Finkle argued that arthritis may sometimes occur with myxedema. Others (Schnitker et al.) have noted "chronic arthritis" occasionally in cases of spontaneous myxedema, and muscular pains in patients with induced myxedema (post-thyroidectomy).

(According to Monroe, 1935, myxedematous patients rarely have atrophic, often have hypertrophic, arthritis. The percentage relationship was too low to justify regarding myxedema a primary factor.—Ed.)

Peers, studying metabolic rates in various arthritides concluded that "the true arthritic is a nonmyxedematous individual." The low metabolic rates seen fairly often in arthritic patients "are not due to a lack of thyroid hormone but are brought about in some other fashion." Tidy



also concluded that neither hypothyroidism nor hyperthyroidism is the primary cause of any chronic rheumatism; even though thyroid extract may help arthritics with low rates, "there is no reason to ascribe any specific action to thyroid."

*"Climacteric Arthritis."* This holds a precarious position in the family of arthritides. It is placed in the classification of the Ligue Internationale Contre la Rheumatisme as synonymous with "endocrine, metabolic, hypoglandular rheumatism; villous arthritis; rheumatic gout; gout in women." The classification of the British Medical Association includes "chronic villous arthritis, mainly occurring in women at or about the climacteric." Neither climacteric nor villous arthritis is recognized by the classification of the British Ministry of Health, nor in the official nomenclature of the Royal College of Physicians. Recently a subcommittee of the Royal College of Physicians listed "climacteric arthritis (villous type)" twice, deciding that it may produce either a "rheumatoid type" or an "osteo-arthritic type" of chronic arthritis.<sup>177</sup> Thus, three views are held: that "climacteric or villous arthritis" does not exist (this view is held by most of us.—Ed.); that it is an entity with special clinical and pathologic features, or that it is an entity which produces now one, now another pathologic reaction.

*Etiology of Climacteric Arthritis.* Seven writers currently expressed their views thereon. Although the majority believed that climacteric arthritis was due to some kind of endocrine deficiency, they were not certain just what kind. The cause is probably hypothyroidism according to Thomson, who nevertheless prescribed pituitary extract also in some cases. à Court noted the disease in florid stout patients "with signs of thyroid deficiency." Gordon considered it "an endocrine deficiency especially of thyroids." Fox did not incriminate endocrines but considered it due to "disturbances of digestion, metabolism and excretion," to "toxic or metabolic factors" due perhaps to "the formation of abnormal substances or to simple failure of excretion."

(Obviously the above writers were very hazy as to the cause. None gave laboratory data indicating a consistent deficiency of ovarian or thyroid function. It should not be difficult for those who believe in the entity to apply to reputed cases the newer laboratory methods for estimating ovarian and other deficiencies. This would do much to settle the argument.—Ed.)

*Clinical Aspects of Climacteric Arthritis.* There was no uniformity in the clinical picture presumably characteristic of "climacteric arthritis." Some regarded it as synovitis, others as arthritis. According to Thomson it "occurs exclusively in middle-aged women, affects the knees and occasionally one or more other joints, such as wrists." It affects knees according to Buckley, knees but also first metacarpal joints according to Gordon. à Court considered it "a gradual increasing stiffness and pain in affected joints, usually the knees." Fox separated "climacteric arthritis" or the "arthritis of middle life" from both atrophic and hypertrophic arthritis.

He regarded it as "different from the much more serious rheumatoid arthritis of the young, on account of its mode of onset and the order in which the joints are affected, its more favorable course, its limitation often to a few joints, and its occurrence in comparatively healthy people." According to him, intermissions of one or two years are not uncommon; after a few years there is comparative quiescence with localization in one or two or a few joints, a "less profound constitutional disturbance, and thus a more favorable prognosis." Incidentally, I have noticed in many cases that the arthritis has been almost or quite confined to the left side of the body." It affects married women, especially those with children, much oftener than the single. The average age of onset in Fox's cases was 48 (range, 37 to 54) years.

Hall's conception of "menopausal arthritis" was much more inclusive. He studied 49 women who developed joint distress coincident with the onset of menopausal symptoms. Of the 49 cases, 23 were "castrates" (two by roentgen-ray, 12 by operation, nine by unilateral oöphorectomy with subsequent "stormy menopause"), 26 experienced a physiologic menopause. Of the castrates, six developed atrophic, four hypertrophic arthritis, 13 "arthralgia." Of the others, 12 developed atrophic, five hypertrophic arthritis, nine arthralgia. Thus menopausal arthritis simulated atrophic arthritis in 18 cases, hypertrophic arthritis in nine cases, "arthralgia" in 22 cases. Unable to determine concentrations of urinary estrin or prolactin A, Hall based his diagnosis of menopausal arthritis on the coincident appearance of menopausal and articular symptoms, but especially on the beneficial effect of estrogenic substances on the former. Joints involved, in order of frequency, were hands, knees, neck, wrist, fingers, ankles and lower back. In marked cases 25 to 50 per cent of all joints were involved. "Arthralgia" consisted of absence of swelling or of marked tenderness, heat, redness, crepitus or altered function; presence of irregular pain, morning stiffness, slight puffiness and tenderness, pains coming and going abruptly, often appearing markedly at night, perhaps due to vascular spasm.

*Pathology of Climacteric Arthritis.* According to Thomson and à Court "proliferative synovitis" is primarily present, with fine crepitations audible and palpable on joint motion. Fox and Gordon considered it different from, but often ending in, osteo-arthritis: "The typical change in the knee joint is a villous overgrowth of the synovial membrane, passing in a few years into a later stage of degenerative osteo-arthritis." Hall's views were noted. To Fletcher the pathologic reaction "may be rheumatoid in type, more usually it is villous or osteo-arthritic."

*Roentgenographic Changes of Climacteric Arthritis.* These were not specifically defined. Scott found no radiologic picture characteristic of "climacteric arthritis."

(We are divided in our views. Most of us do not recognize it as an entity, believing that it is a mild senescent hypertrophic (degenerative) arthritis with or

without its commonly associated fibrositis, or that it is atrophic arthritis in a patient at the menopause. Its supposed pathology of primary and dominant synovitis, later associated with degenerative changes, presents a hybrid between that of atrophic and hypertrophic arthritis, or else represents a mixture of the two, the synovitis of mild atrophic arthritis coincidentally or subsequently associated with the inevitable degenerative changes of hypertrophic arthritis. Matters could be distinctly clarified if the protagonists of the entity would present pathologic data on "typical cases." Do they present synovial pannus formation, lymphocytic collections characteristic of atrophic arthritis, and the cartilage changes of atrophic arthritis; do they demonstrate the usual picture of hypertrophic arthritis, or do they present a specific and unusual type of synovial and cartilage involvement?—Ed.)

*Treatment of Climacteric Arthritis.* Usual treatment was thyroid extract, weight reduction, correction of posture and flat feet.<sup>118, 181, 546</sup> Iodine and pituitary extract were recommended.<sup>546</sup> Fox, believing it a metabolic, not an endocrine, disturbance, did not recommend endocrines but general measures to promote elimination and reduce strain. The osteo-arthritic stage can be prevented, according to Gordon: "If properly treated by increasing the local synovial activity, by heat, and other means, and by redressing the endocrine deficiency, especially that of the thyroid, the original arthritic process can be cured before any osteo-arthritis has supervened." Without details Fletcher recommended estrogenic therapy.

Intramuscular injections of theelin or progynon controlled menopausal symptoms in all of Hall's 49 cases. From 50 to 100 per cent of relief in joints was noted in 91 per cent of the 22 cases of arthralgia, 66 per cent of the 18 with atrophic and 44 per cent of the nine with hypertrophic arthritis. Treatment and results differed in the castrates and those with a physiologic menopause. Individual doses varied from 200 to 2000 rat units (1000 to 10,000 International units). Some received 6000 rat units weekly. Relief (50 to 100 per cent) of joints was experienced by 82 per cent of the castrates, by 65 per cent of the others. The former required more than 2000 rat units in oil per week; noncastrates required 2000 rat units or less weekly. Usually at least six doses were necessary, doses being given at five to seven day intervals.

*Acromegalic Arthropathia.* Human "acromegalic arthritis" has been noted (for example, Erdheim, 1931). Silberberg produced its pathologic counterpart in guinea-pigs by injecting an acid extract of cattle anterior pituitary gland. First noted were hypertrophy and hyperplasia of cartilage cells, first in the transitional, later in the sliding and pressure zone. This proliferative process was then followed by liquefaction and degeneration of the growing cartilage, with ulceration of its surface. Calcification of cartilage was later noted. Since similar or greater changes were produced in thyroidectomized guinea-pigs, the pituitary extract obviously acts without intermediation of thyroid.

*Arthritis and Parathyroids.* The arguments of those few physicians who "without good evidence" attempted to relate arthritis to hyperparathyroidism have been about silenced. Wooton argued relationship, not di-

rect but indirect, between various articular diseases and parathyroids. His "commonplace viewpoint" is very hypothetical and fanciful, with absolutely no scientific proof to support it. Reviewing past arguments favoring a relationship, Jessop, Wilder and Howell, Parsons and others agreed that none of the arthritides have any proved connection with hyperparathyroidism. Apparently considering the argument "closed" or fruitless, most current writers on hyperparathyroidism did not even mention joints.

Although the skeletal pathology in clinical hyperparathyroidism is osseous, not articular, it behooves rheumatologists to be familiar with hyperparathyroidism because of its frequent "rheumatic-like" symptoms. The disease characteristically produces skeletal aches and pains, particularly in the back (72 per cent).<sup>53</sup> The osteoporotic form of the disease (the early stage of the classic type without cysts or bone tumors, when symptoms are produced by generalized decalcification) is often diagnosed "rheumatism." One should suspect hyperparathyroidism in patients with generalized "rheumatic" or "neuritic pains" or with unexplained arthritic pains of the nerve root type,<sup>53, 333</sup> but *only* if they (repeatedly) exhibit the classical chemical features. In hyperparathyroidism blood calcium and phosphatase and urinary calcium and phosphorus are high, blood phosphorus is low. In chronic atrophic and hypertrophic arthritis the blood and urine calcium and phosphorus are generally normal and blood phosphatase is normal or slightly low.

Several of the recent cases of proved hyperparathyroidism presented "rheumatic" symptoms.

One patient's chief complaint was pain in feet, legs, and back, seemingly affected by weather, and the condition was treated as "rheumatism" for six months.<sup>568</sup> Another had weakness and severe pains in arms, lumbar region and legs called "sacro-iliac strain and sciatica."<sup>17</sup> The aches and pains of one had been called "arthritis"; another had pain and tenderness of a sacro-iliac joint, limited motion of spine and a tender hip.<sup>86</sup> One case of severe pain in neck, back, and both legs was labelled "neuritis" for eight years.<sup>283</sup>

Others noted pains in back and shoulders on motion,<sup>283, 436</sup> but specifically stated that the pains were not in joints. In three cases of Merritt and Lattman, articular complaints were noted: one patient had a painful swollen knee with cystic bone destruction at the distal end of the femur; another had a painful shoulder, hip and back; the third had painful, tender hands, forearms and shoulders called "chronic arthritis" by a leading rheumatologist.

(We cannot be sure that these three cases were of hyperparathyroidism. Chemical studies were incomplete or not done; biopsy was not made; the patients were treated by roentgenotherapy.—Ed.)

Injections of parathormone in rats produced osseous and other lesions characteristic of clinical hyperparathyroidism but no articular lesions (Johnson, 1932). Animals fed large doses of vitamin D will also develop similar osseous changes and metastatic calcification. In addition to these, however, Fang and Miltner noted degeneration and calcification in articular cartilage and intervertebral disks (lesions not noted in clinical hyperparathyroidism). The lesions disappeared after administration of vitamin D was stopped.

For those interested in the general subject, its clinical types, chemical and radiologic differentiation, urologic features, complications and treatment, several other excellent reports are available, in particular, Wilder and Howell's summary of 135 reported "proved cases." 42, 74, 204, 212, 268, 304, 378, 386, 411, 412, 426, 436

*Chemical "Arthritis" or Arthralgia.* Arthritic patients receiving thyroid extract sometimes note increased joint symptoms, presumably due to heightened sensitivity and lowered threshold for pain. However, nonarthritic patients with myxedema, or with low basal rates without myxedema, commonly develop generalized arthralgia and particularly myalgia (influenza-like) for a few days shortly after starting thyroid therapy (Plummer and Boothby, 1927). One of the toxic manifestations of excess alkali therapy for duodenal ulcer is aching pain ("grippe-like") in muscles and joints (Hardt and Rivers, 1923). Such forms of toxic myalgia and arthralgia might be designated myalgia or arthralgia medicamentosa. Genner has used the term "paratherapeutic articular disturbance" to indicate articular symptoms from antisyphilitic treatment. Of 2235 patients under such therapy, 79 (3.5 per cent) developed articular disturbances, usually polyarticular, generally only arthralgia, occasionally with slight swelling and redness. Symptoms sometimes lasted months after therapy was stopped. In two cases severe arthralgia necessitated hospitalization. Bismuth, not arsphenamine, was held generally responsible. Of patients with arthralgia, 42 per cent were receiving bismuth alone, 54 per cent arsphenamine and bismuth, and only 4 per cent arsphenamine alone. Common signs of bismuth intoxication were jaundice (116 cases) and erythema (148 cases). Although jaundice and arthralgia usually did not occur together, the combination was noted in 10 cases, jaundice appearing before the pain in three, after the pain in seven cases.

(No note was made on intensity of jaundice or any ameliorating effect of this type of jaundice on joint pain.—Ed.)

Wolf (1925) believed the arthralgia was caused not by a direct toxic effect of the medicine on joints but by an indirect effect through impairment of hepatic function, so that noxious autolytic products enter the blood stream and produce, among other effects, articular pain. Genner favored a "direct toxic-medicamental effect" in spite of the frequency of hepatic symptoms. "The individual tolerance is dependent on the detoxicating power of the organism (largely dependent on hepatic function) and on the functional capacity of excretory organs. When these safety valves fail to work properly, toxic by-effects appear."

#### MISCELLANEOUS TYPES OF JOINT DISEASE

*Synovitis; Transitory Synovitis of Hip Joints.* Children under eight years of age are affected. Finder saw 22 cases subsequent to 1916. Symptoms were a limp, pain frequently referred to knees, night cries, restlessness,



often slight fever and leukocytosis. Since synovia alone was involved, roentgenograms were negative. Presumed causes were trauma and infection. Treatment included rest, traction, sometimes immobilization, physical therapy. "The outcome is uniformly good."

(May these not be cases of atypical atrophic arthritis?—Ed.)

*Tenosynovitis.* Spencer reviewed features of the traumatic, suppurative, gonorrheal, syphilitic, tuberculous, and "rheumatic" types. Early and adequate incision is necessary in synovial whitlow (suppurative tenosynovitis).<sup>460</sup> Cohen's patient with "tenosynovitis crepitans" of a wrist, precipitated by trauma, unrelieved by rest and physical therapy, had oxaluria and had had an oxalate renal stone. Measures to stop oxaluria (special diet and medicines) relieved wrist pain within three weeks. Six other patients responded similarly. Patients refused biopsy. Cohen recommended metabolic studies and this treatment in similar cases.

*Stenosing Tendovaginitis: DeQuervain's Disease.* Occupational trauma produces "snapping thumb or finger" caused by a localized thickening of the tendon as it passes with effort through a partially stenosed tendon sheath. Tendons themselves are usually normal. Although not uncommon, only 200 cases have been reported. Thirty-five new cases were noted (Burns and Ellis; Patterson; Zelle and Schnepf). A thumb is usually affected, with slight swelling and marked tenderness over the radial styloid. Voluntary abduction or forcible adduction of the thumb is painful. Conservative treatment is generally unsuccessful. "Immediate relief" is obtained by simple incision of the constricting sheath.

*Intermittent Hydrarthrosis.* It is uncertain whether this is a pathologic, or a peculiar physiologic, reaction of the articular lining or of those elements which produce synovial fluid. Pathologic reactions in one case were slight thickening of the lining layer of cells without increased fibrosis or perivascular thickening (Ghormley and Deacon). In Collin's case the total synovial cell count was 1600 per cu. mm. in one knee, 2500 in the other with 58 and 71 per cent polymorphonuclears.

*Synoviomas.* Black described a benign synovioma arising from a tendon sheath or bursa of a hand following injury. Its cells produced a mucinous fluid resembling synovial fluid. Early symptoms of malignant synoviomas may resemble those of "arthritis." Synovial sarcomas are rare: Knox reported 19 cases from the literature and three new ones. Knee joints were affected nine times. First symptoms were swelling, tenderness and pain, usually before, occasionally after, the appearance of a mass. They rarely arose in arthritic joints. Malignant tumors of joints, bursae or tendons are fibrosarcomas or synovial sarcomas. The latter are resistant to radiation, not cured by amputation.

*Chondromas.* These were classified by Moore as (1) simple: ecchondroma, enchondroma; (2) compound: osteo-, fibro-, myo-, angio-, papillary-chondroma, (3) malignant: chondrosarcoma. Simple or malignant second-

ary changes may develop, in order of frequency: calcification, ossification, fatty degeneration, mucoid softening, cystic degeneration, surface ulceration, sarcomatous degeneration, chondroma-sarcoma. Baker discussed osteochondromas, the commoner type. A case of chondroma of the head of the fibula, described by Moore, was regarded most unusual because "few parts of the skeleton are so seldom the site of pathologic affections and anomalies as the proximal end of the fibula." Multiple loose bodies in joints most often arise from synovial osteochondromatosis, a metamorphosis of synovial membrane into a benign tumor.<sup>194, 195</sup>

*Hypertrophic Pulmonary-Osteo-Arthropathy.* A case with usual features was seen by Kline; the patient was a boy with pulmonary tuberculosis.

*Arthritis and Scleroderma.* A child developed cicatrizing morphea (circumscribed scleroderma) over buttocks, legs, abdomen. A few months later pain and tenderness involved knees, hips and ankles without swelling or inflammation. Ankylosis of hips, flexion of knees, stiffness of feet, bone atrophy and calcium deposits in patellar ligaments and Achilles' tendon ensued (Crawford).

*Supratrochanteric Calcification.* Calcified deposits near the greater trochanter may cause pain and disability of a hip. Such deposits were found by Goldenberg and Levinthal in none of 100 patients under 15 years of age, in 30 (5.4 per cent) of 550 patients over 15 years; 20 affected the gluteus medius tendon, eight the bursa between the tendon of the gluteus medius and the greater trochanter, two the under surface of the gluteus medius. Reflex spasm of the latter limited abduction and internal rotation of the hip. The condition is analogous to that affecting the supraspinatus muscle in "sub-acromial bursitis." Surgical removal of deposits provides a cure.

*Miscellaneous Conditions.* Conditions which give rise to symptoms which imitate arthritis were discussed by Kerr: syphilitic dactylitis, bursitis, myositis or periostitis; scurvy, beriberi, rickets, Raynaud's disease, leprosy, cervical rib and the *scalenus anticus* syndrome; erythralgia, peripheral neuritis.

(One might add lupus erythematosus, periarteritis nodosa, and others.—Ed.)

Early symptoms of spinal metastatic carcinoma from the prostate are often considered arthritic. In Duncan's 85 cases with secondary growths in pelvis and spine, pain was usually worse at night, better when patients got up and walked. Spinal motion was freer than in arthritic patients. Rosh noted cases of Hodgkin's disease with vertebral involvement.

#### DISEASES OF MUSCLES, AND FIBROUS TISSUE; FIBROSITIS

Fibrositis denotes swelling and proliferation of white fibrous tissue anywhere in the body in response to injury and various toxic influences, with the secondary effect of pressure on arterioles and nerve filaments.<sup>475</sup> It is no more one disease than is arthritis. On the basis of supposed cause,

Slocumb noted these etiologic types: (1) primary fibrositis—unaccompanied by and independent of, any other definite disease; (2) secondary fibrositis—that secondary to some known cause or primary dominant condition such as trauma, gonorrhea, rheumatic fever, gout, hypertrophic or atrophic arthritis. This groping for order indicates a present knowledge of fibrositis inferior even to that of arthritis. Probably half the symptoms of hypertrophic arthritis are due to associated "senile fibrositis" according to Hunt and Gordon who believe it is due not to foci of infection but to a metabolic fault from impaired circulation and faulty elimination. Treatment of fibrositic nodules, so common with atrophic arthritis, will give some relief (Wilson). The gouty nature of some forms of fibrositis and lumbago was suspected.<sup>151, 360</sup>

*Primary Fibrositis.* This condition, of unknown cause and independent appearance, is the most common type, "the commonest form of acute or chronic rheumatism" (Scott, Slocumb). Almost everyone suffers with one of its forms at least once in his life. Telling called it perhaps the commonest cause of persistent and recurring pain. Copeman and Slocumb noted the two stages of the lesion: the early acute stage of effusion, a mild or severe localized inflammatory (serofibrinous, not cellular) exudate perhaps seen as a puffy swelling; the later stage of organization, with the production of fibrous thickening, nodules and cords.

The anatomic types were listed<sup>102, 405</sup>: (1) intramuscular ("muscular rheumatism," "myositis," "myofascitis"); (2) periarticular (capsular) fibrositis ("capsulitis," "capsular rheumatism"), (3) bursal fibrositis, "bursitis," (4) tendinous fibrositis, for example, palmar or Dupuytren's fibrositis; (5) panniculitis, fibrositis of subcutaneous tissue; (6) perineural fibrositis, "interstitial neuritis," for example, some forms of sciatica and brachial neuralgia.

*Symptomatology.* This was reviewed by Slocumb and Copeman. Considering differences in situation of the disease it is obvious why symptoms are so protean. The common characteristic symptoms of the various anatomic types were aching, stiffness and soreness, particularly when the part is put on a stretch; little or no objective changes except the palpable indurations; much fatigue, chilliness and general hypersensitivity. Many cases of indurative headache, lumbago, low back pain and intercostal neuralgia are of fibrositic origin, also many cases of "central or interstitial sciatica."<sup>3, 102, 150, 558</sup>

In sciatic fibrositis, pain is referred to the hamstring muscles and not to the nerve trunk, which is not even tender until later; reflexes are normal and anesthesia and paresthesia are absent.<sup>102, 150</sup> Albee considers myofascitis the commonest cause of pain low in the back where there are so many fascial insertions into bone and "a more sluggish circulatory condition than elsewhere." (But the blood supply of the back is rich.—Ed.) Panniculitis, a fibrositis of subcutaneous fibro-areolar fatty tissue, is characterized by disseminated superficial pea-like nodules, so that the skin wrinkles or puckers

when grasped between the hands. The tissue is fatty, tender, and bruises easily. Normal fat is not tender or lumpy. These and other features of panniculitis were described by Telling.

*Pathology.* Data thereon are meager because biopsy is not often made; when made it reveals a vague pathologic picture. Information is available concerning the nodules but not concerning the reaction responsible for such varieties as capsular fibrositis. Sections of nodules from early cases of lumbago show, according to Douthwaite, no recognizable difference from the normal surrounding structures. They give the microscopic appearance of normal excised muscle, since they represent a gel or local coagulum with no cellular infiltration; yet "the nodule is a very real thing." Even chronic lesions reveal no characteristic or striking architectural arrangement, like Aschoff nodules, but are vaguely described as "unhealthy fibrous tissue," "inflamed scar tissue" (Copeman). Certain nodules are not tender; hence some ignore them as of no significance, particularly because experienced persons can feel free nodules in "normal persons." They are not normal but, according to May, always evidence of a previous attack of (sometimes subsymptomatic) fibrositis. Even the nontender ones are potentially troublesome.<sup>208</sup> They are often difficult for the inexperienced to palpate. Cases of lumbar myofascitis with palpable nodules are in the minority, according to Albee, who failed to find measurable increases of thickness in affected regions. The more severe cases of fibrositis reveal the most nodules, tender or otherwise. They are usually tender, especially when a nerve twig is implicated, often exquisitely so; when they are pressed the patient squirms and muscles go into spasm. To Douthwaite they do not represent septic emboli; if they did, massage would only aggravate the condition. But for the very reason that firm massage of nodules does often produce slight fever and malaise within 24 hours or so, Scott and Wilson believed they must contain bacteria, probably streptococci and toxins, not toxins alone. Even breaking down old hard nodules is likely to produce reactions. (No data on cultures were given.)

(Most American clinicians have been loath fully to recognize "fibrositis," because its supposed pathology is so ill-defined, its symptomatology so subjective, its chemical reactions "normal." Others who recognize it as a distinctive symptom-complex worthy at least of clinical separation, are nevertheless disturbed by its insecure pathologic basis. Those numerous physicians who, particularly in England, continue to write familiarly of the pathology of fibrositis would immeasurably strengthen their position if, instead of merely briefly restating oft-repeated comments, they would present formal studies with microphotographs showing, as well as possible, the vague reactions which are considered so basic. Until then they cannot escape the suspicion of being guilty of merely repeating what they have read. Many have obviously accepted the work of Stockman (1920) but in the past 20 years of English "fibrositology" few if any have formally attempted to corroborate or advance that work.—Ed.)

*Laboratory Data.* The sedimentation rate is generally normal.<sup>493</sup> Stuart-Harris found no antifibrinolysins. In stools, Albee found "his-

tamine in large quantities"; to him an index of toxicity, possibly an etiologic agent.

(No quantitative data were given.—Ed.)

*Differentiation.* Slocumb studied 100 patients with periarticular and intramuscular fibrositis, the commonest forms.

About 50 per cent of the patients had both types concurrently or consecutively; 25 per cent each had one or the other type alone. Since many cases of periarticular fibrositis are erroneously called "mild atrophic arthritis" (with its malevolent connotations) differentiation is important. The 100 cases of long chronic fibrositis (total disability 284 years, selection being made to allow maximal local and constitutional changes) were compared to 100 cases of atrophic arthritis, early cases being chosen to see how early the local and constitutional differences would be apparent. Both groups experienced fatigue and nervous exhaustion. Ten pounds or more were lost by 47 per cent of the arthritics, by only 7 per cent of the fibrositics. Roentgenograms were "definitely positive" in 86 per cent of the arthritics (although 50 of them had had their disease less than a year), in none of the fibrositics (except those with occasional incidental senescent hypertrophic arthritis). The sedimentation rate averaged 12 mm. (1 hour) in the fibrositics (below 16 mm. in 73 per cent, never over 32 mm.), 72 mm. in the arthritics (normal in only 6 per cent, over 25 mm. in 91 per cent, over 50 mm. in 67 per cent). Rates were usually elevated within the first six weeks of arthritis. Hemoglobin was below 13 gm. in only 5 per cent, below 12 gm. in only 1 per cent of the fibrositics; below 13 gm. in 42 per cent, below 12 gm. in 19 per cent of the arthritics. Occasional patients with periarticular fibrositis exhibited one of these abnormalities, very rarely more; most of the arthritics exhibited two or more definite, not slight, alterations.

In summary, periarticular fibrositis is readily differentiated from even early atrophic arthritis by the characteristic and persistent negativity of clinical, laboratory or roentgenographic evidence of intra-articular disease or constitutional reaction.

Cases of left-sided thoracic intramuscular fibrositis are occasionally called angina pectoris. Some recognize "mural fibrositis" of the abdominal musculature, often mistaken for intra-abdominal disease. According to Wilson, pain referred to the abdomen results particularly when fibrositic nodules involve the eighth to the eleventh intercostal spaces. Motion of these muscles may or may not cause pain. Differentiation often depends on finding tender intercostal nodules, pressure on which produces immediate referred abdominal pain "or an attack of abdominal pain delayed for some hours or even a day or two."

*Etiology.* The cause of primary fibrositis is unknown. The usual conjectures were entertained: infection<sup>276</sup>; strain and chill<sup>3, 69, 102, 106, 151</sup>; "metabolic disturbances"<sup>69, 150</sup>; "toxicity from intestinal infection or poor elimination"<sup>3</sup>; "oxaluria."<sup>276</sup> Generalized fibrositis is probably an infection; chills and strains produce localized fibrositis.<sup>150, 151, 276</sup>

(Reading current reports we, with Milliken, were "left a bit vague as to whether myofascitis is due to focal infection, the phases of the moon, or the Hoover administration."—Ed.)



*Treatment.* For acute fibrositis the majority favored rest and heat. If the patient is brave, Douthwaite recommended, even in acute cases, vigorous motion of the affected part for 20 minutes; "great, sometimes complete relief is obtained in half an hour." In lieu of active motion, massage was given. English writers again emphasized the "supreme importance and curative value" of their favorite remedy, deep massage "to rub away the nodules." "The only effective cure," it is more useful if preceded by heat (Cruickshank). No other treatment is of such value; the fibrotic change must be treated mechanically; treatment may be painful, tedious and prolonged (Telling). "Break down the fibrous nodule and liberate the imprisoned toxins," to be then eliminated by improved circulation. Specially trained masseurs can do this; although it is painful they must persevere and not be alarmed by the patient's easy bruising (Gordon). Hunt approved the continental axiom: no cure without bleeding. "Massage must therefore be progressively stronger and deeper, and may be energetic enough to cause actual hemorrhages around the nodule." Douthwaite also advocated "deep massage which will probably make the patient yell."

When such massage is too painful preliminary histamine ionization may be useful.<sup>102, 106</sup> Wilson who of all wrote the most enthusiastically and in greatest detail on the technic and value of manipulative massage to break up the fibrotic nodules, claimed that in some cases it "will in a few minutes relieve pain that has for many years accompanied certain movements of a joint." "Localized tenderness . . . can be made to disappear within a few minutes." Because such massage may "produce a liberation of toxin" and a reaction of fever and malaise within 24 to 48 hours, Wilson and Scott advised that a limited number of nodules be massaged at one session, and massage be given only every three to five days. For old nodules too resistant to be "destroyed" by finger pressure, Wilson described a technic utilizing the sharp but protected blows of a wooden mallet. Manipulation and massage under anesthesia may cure certain cases of chronic lumbago "within five minutes," according to Douthwaite.

(From a limited experience with manipulative massage we cannot match the enthusiasm of our English colleagues, but American clinicians must use this treatment more extensively to criticize it authoritatively.—Ed.)

Numerous other measures were recommended: Triple typhoid vaccine, streptococcal vaccine, injections of a local anesthetic or even simple needling of a nodule<sup>102, 106</sup>; injections of saline or quinine urea hydrochloride<sup>348</sup>; bee-venom<sup>57, 397</sup>; histamine by injection or ionization<sup>57, 102, 106, 157, 396, 481</sup>; colonic lavage<sup>3, 102, 106</sup>; dietary and medicinal correction of oxaluria; acidophilus milk; warm climate, low carbohydrate diet; a raw vegetable diet.<sup>237</sup> Gold is valueless.<sup>14, 102, 106</sup> (A refreshing statement.—Ed.) Scott noted "a more or less complete disappearance of local disability in 18 out of 25 cases" of intractable fibrositis, usually of 10 or more years' duration, from local injections of a "lipovaccine" (streptococci suspended in olive oil) into nod-

ules. A local and general reaction like that from heavy massage was induced within a few hours. "Persons who had been in poor condition for years regained their normal color and appearance in a week or two"; symptoms abruptly subsided, leaving the fibrositic region comparatively painless.

To avoid the common local fibrositis in the neck and shoulders presumably caused by wearing too heavy coats, heavy clothing outside and evening gowns inside the house, with consequent trauma and chilling, Burt recommended warm, but light, clothes, and adequate sweating. "Skin-toughening cold showers" may be prophylactic.<sup>360</sup>

*Dupuytren's Contracture.* This starts as a firm, fixed nodule in palmar fascia, usually near the base of the ring finger, affects fascia, not tendons, and is generally eventually bilateral. Of Meyerding's 273 patients, 45 per cent were physical, 55 per cent mental, workers; 88 per cent were males; age of onset was 17 to 80 (av. 54) years. Of 273 patients with 448 affected hands, both hands were involved in 64 per cent, the right alone in 25 per cent, the left alone in 11 per cent. Fasciotomy is generally inadequate. Palmar fasciotomy gave "excellent results" in 89 per cent of 117 hands. Postoperative treatment included use of splints, heat, early motion, more active physical therapy after the fourth week.<sup>364, 365</sup>

*Epidemic Diaphragmatic Pleurodynia.* The "devil's grip" is spreading westward in the United States: epidemics were noted in late summer and fall of 1934 and 1935: 72 cases in Illinois<sup>368</sup> and 22 in Colorado,<sup>401</sup> the first two west of the Appalachian Mountains and Mississippi River; 11 cases in Cincinnati<sup>367</sup> and 282 in southwestern Ohio.<sup>235</sup> A few patients noted prodromes: fatigue, vague abdominal cramps. Onset was usually abrupt, with sudden, severe pain in the region of the diaphragm (more often on its thoracic than its abdominal side), lower thoracic wall, often the entire costal margin, also in the epigastrium and upper abdomen. Pain shifted from side to side and came in repeated paroxysms (two to nine in all). Sometimes present was pain in back, shoulders, head and neck. Other symptoms were fever (100° to 104° F.), rapid pulse; leukocytes 3000 to 10,000, no eosinophilia; pallor; nausea; sweating; occasional diarrhea and chill. Deep breathing was painful. Pain and fever lasted 24 to 36 hours, occasionally three or four days; maximal pain was often between the fourth and twelfth hour. The third paroxysm was usually the most painful. After three or four days of quiescence a second short attack may appear. Friction rub was generally absent (often present in European cases). When abdominal pain is severe, differentiation from "acute abdomen" is difficult; pain may be over McBurney's point but is generally higher and bilateral; the abdomen is fairly relaxed. The condition is also mistaken for pleurisy, herpes zoster, coronary thrombosis. Recovery was usually rapid and complete. Complications were rare (orchitis once).<sup>368</sup> Treatment is symptomatic; morphine is required. The cause is unknown. Small's (1924) plasmodial theory was not confirmed. The disease is communicable, incubation period being

three to seven days. Blood cultures in six cases were sterile; biopsy of the latissimus dorsi muscle was "negative."<sup>567</sup> Age, sex and social status seemed unimportant. Because it occurs in the mosquito season and nearly every one of his patients recalled a recent mosquito bite, Naugle suspected a mosquito-borne disease.

*Myositis Ossificans.* Commonest sites for the traumatic form are the brachialis anticus from injuries about elbow, the quadriceps femoris from "Charley horse," the abductor muscles in horsemen, the deltoids in infantrymen from gun-butt trauma, and the biceps brachii. Hobart noted nine cases. Hamada treated a young girl with myositis ossificans progressiva multiplex.

*Calcified Intramuscular Parasites.* These, presumably cysticercus cellulosae, produced countless discrete, ovoid shadows  $\frac{1}{8}$  to  $\frac{1}{2}$  inch in size throughout the extremities, abdomen, chest. Muscle biopsy was refused (Lesoff and Schulman).

*Trichinosis.* Asymptomatic trichinous myositis must be very common. At necropsy, McNaught and Anderson found living larvae in 24 per cent of 20 human diaphragms from persons aged 2 to 87 years. The number of larvae was less than 20 per 50 gm. of muscle in 79 per cent. No patient had had clinical trichinosis.

*Melitensis Infection of Muscle.* A case of degenerative myositis with temporary muscle atrophy from Malta fever was noted (O'Donoghue and Scott).

*Myopathies and Neuromuscular Disorders.* Further studies on metabolism of creatine and creatinine in myopathies were presented<sup>247, 366</sup>; also electromyographic studies in hysterical torticollis, Huntington's chorea, paralysis agitans.<sup>346</sup> The use of amino-acetic acid (glycocoll, glycine) was recommended not only for primary myopathies but also to relieve fatigue and creatinuria of muscle disturbances secondary to such conditions as nephritis, scarlet fever, hyperthyroidism, anemia, hyperinsulinism (Terhune and Green).

#### DISEASES OF BURSÆ

The four intermetatarsophalangeal bursae have been ignored in literature: bursitis in one was noted.<sup>343</sup> In Snodgrass' case of compound cystic bursitis of a knee, the suprapatellar bursa and that in the gastrocnemius muscle were connected and both enlarged.

*Subdeltoid and Subacromial Bursitis.* Of the 140 bursae in the body (33 in each upper, 37 in each lower extremity) the subdeltoid is most often diseased (Echtman). Of 300 consecutive painful shoulders studied by Haggart and Allen 80 per cent were caused by subacromial bursitis, 6 per cent by arthritis, 8 per cent by myofibrositis, 6 per cent otherwise. In Lee's cases, trauma seemed to be a factor in 50 per cent, the right shoulder was affected twice as often as the left, 75 per cent of patients were males. Many cases of Weeks and Delprat were preceded by upper respiratory infections. Current ideas on etiology, differential diagnosis and therapy were reviewed.

Echtman first applied cold applications, then heat, massage and manipulation; diathermy for cases with calcification; for stubborn cases galvanization or ionization with magnesium sulphate. Lee used immobilization in abduction and external rotation, surgical removal of chronic painful calcium deposits. Lattman stated that roentgen therapy relieves pain and restores function faster than anything else: good results were noted in 15 of 20 cases; one or two treatments reputedly relieved pain in 24 to 48 hours. Rapid relief may follow simple aspiration of bursal fluid; even the mere procedure of needling (multiple punctures at one session) is often helpful whether calcium deposits are present or not (Weeks and Delprat). Haggart and Allen advised: for acute bursitis, exploration and drainage of the calcified material or procaine injection; for chronic bursitis, physiotherapy, exercises (diagrammed), occasionally procaine injections; for chronic adhesive bursitis, drainage of calcified material, manipulation to loosen adhesions, or procaine injections, physical therapy, exercises. The latter cases without calcification may need elevation and traction in a Balkan frame.

(Calcium deposits often rapidly disappear spontaneously. Their surgical removal should be advised with caution.—Ed.)

#### OTHER STUDIES

*Articular Roentgenography.* The "articular space" as referred to by roentgenologists is a misnomer; it is not the true space but translucent interosseous material, cartilage and ligaments. With improved technic, Widmann and Stecker visualized the true articular space in normal knees and shoulders, not elsewhere. Friedman described an improved roentgenography to show hip joints laterally.

*Arthroscopy.* Further observations on the technic and value of arthroscopy and punch biopsy were reported (Burman, Mayer and Finkelstein). The procedure was technically successful and caused little or no articular reaction, but diagnoses on specimens obtained at biopsy did not always conform to those later made at surgical operation.

*Articular Function.* A method for measuring and recording joint function was described (Cave and Roberts). Jones applied engineering principles to the study of human joint lubrication and determined coefficients of friction of interphalangeal joints. The usual form of lubrication of human joints is by a fluid film which survives a load which can crush bone.

*Articular Physiology.* The metabolic requirements of articular tissues must be known before one can properly discuss the problem of articular nutrition. Bywaters studied the metabolism of normal and abnormal cartilage and synovia.

Cartilage possesses slight but definite glycolysis which, per cell, is similar to that of rabbit liver or kidney. The  $\text{CO}_2$  present all comes from lactic acid. Glycolysis was inhibited by fluoride, increased by phosphate. Oxygen consumption of cartilage was small but greatly increased by methylene blue. The metabolism of synovial

membrane is about the same as that of other adult tissue. Transformations affected by synovia seemed similar to those of ordinary connective tissue except for its very low respiratory quotient for which there is no comparable figure. Inflamed villi have an increased metabolism out of proportion to cell increases. The metabolism of cartilage and synovia is similar in humans and horses. The cartilage metabolism of a horse with degenerative arthritis, and of a woman with atrophic arthritis was normal. Synovial fluid contains twice the amounts of glucose necessary for cartilage.

(For a better understanding of articular diseases many such studies are necessary.—Ed.)

The growth mechanism of articular cartilage as seen in animals of various ages, involves cell division, mitotic in the young, amitotic in older ones. Elliott regarded amitosis an active process of tissue proliferation, not the result of mechanical insults, degeneration or mere necessity of increasing nuclear surface.

Further studies were made on the rôle of the reticulo-endothelial system in the deposition of colloidal and particulate matter in articular cavities (Kuhns and Weatherford). Colloidal and particulate matter is carried by blood to joints from various body tissues, skin, the gastrointestinal tract. It is stored chiefly in histiocytes in synovia, also in bone marrow, lesser amounts in intermuscular septa and articular fat pads. Mild inflammation in joints increases the deposition of such transported substances. Local blocking of the reticulo-endothelial system is transitory, incomplete, and ineffective in preventing deposition of colloidal and particulate matter in joint tissues.

*Muscle Physiology.* Studies on electrolyte changes in muscles during activity<sup>171</sup> and on the circulation in striated and plain muscles in relation to activity<sup>6</sup> were reported.

*Physiology of Tendons.* Cronkite studied the tensile strength of 294 human tendons from cadavers and autopsy material. Certain errors of technic were inherent in methods used. Tensile strength ranged from 8700 to 18,000 pounds per square inch of surface. Right- and left-sided tendons did not vary in strength, nor did flexor or extensor tendons of hands. No one tendon in the body was consistently strongest. There was no correlation between tensile strength and age or cause of death. A historical note on the origin of the term "tendo Achilles" appeared (Couch).

*Additional.* Of interest also were studies by Steindler on physical properties of bone, by Bierman on skin temperature as affected by various physical and chemical factors: age, fever, disease, heat, cold, anesthesia, drugs, tobacco, whiskey, humidity, air motion.

#### CAMPAIGN AGAINST RHEUMATIC DISEASES

The caliber of much of the work reported herein permits one to agree with Weil that rheumatology is no longer "that cloaca of ignorance" so scornfully referred to by Haygarth. The brightest side of rheumatism is the growing interest physicians are taking in it. They realize the necessity



of meeting its challenge instead of sidestepping it.<sup>578</sup> Often the family physician, working with consultants and social agencies, will find at hand adequate facilities for managing his arthritic patients. But the army of arthritic and cardiac cripples attests the inadequacy of our attack. Although in the United States there are more cases of chronic arthritis and "rheumatism" than of cancer, tuberculosis and heart disease combined, and although almost every state and county has a special institution or other facilities for treating tuberculosis, not a single county or state in the United States has a special institution for the care of arthritics except Boston which has the Robert Brigham Hospital.

(However, many hospitals and clinics have departments for the special study and care of arthritics.—Ed.)

From a survey of 89 hospitals, Kling concluded that none of the institutions, city or county, general, church, university or even orthopedic hospitals, are extending adequate facilities to arthritic victims. All gave very low admission rates for arthritics (0.85 to 2.3 per cent). There are about 646,000 tuberculous patients in the country of which 363,000 are bedridden. To the 87,000 beds available for them, about 156,000 tuberculous patients are admitted annually. In other words, one of every four sick or one of every two bedridden tuberculous patients is provided with institutional care, generally for the duration of active disease. In contrast, hospital facilities were available for less than 10 per cent (98,000) of our 1,020,000 bedridden rheumatic patients. About 90 per cent of beds for the tuberculous are free; very few free beds are available for arthritics. Physicians in charge of tuberculosis devote themselves largely to this disease, but most rheumatic patients are cared for by "physicians with little interest and very inadequate facilities." There is therefore great need for state sanatoria or community funds for hospitals and teaching centers to care for and rehabilitate those persons unable to attend spas and health resorts, and to allow study of all aspects of these diseases.<sup>181, 269, 329</sup> But to avoid a narrow viewpoint, rheumatism centers should be established in connection with general hospitals and general clinics, not as segregated institutions for arthritis (Irons).

In England also the few existing facilities merely touch the fringe of the problem, which must be attacked as was that of tuberculosis. England must have a changed outlook, and realize that rheumatism, although chronic, is an acute problem (Elman). In that country the disease is largely unchallenged. The Red Cross Society Clinic in London is "the only one in England solely devoted to treating rheumatic diseases." Copeman reviewed its activities: 80,000 to 90,000 patients (visits or registrations?) are seen yearly. "Every city and industrial center in England should be a candidate for such a clinic." Other angles of the campaign were outlined in Horder's report of the activities of the British National Society for the Control of Arthritis, and in Van Breemen's report of the organization, function and aims of the International League against Rheumatism.

Denmark and Sweden are courageously facing the problem. Kahlmeter regarded the value of Sweden's specialized hospitals self evident. Various other methods were adapted to bring rheumatic diseases under control: institutions for research and for the training of rheumatism specialists, consultation clinics for rheumatic patients allied to hospitals and physical therapy units, proper development of spas, utilization of social service departments.

Noting the meager instruction on joint diseases given to medical students, Johnson believed instruction should be the duty of clinicians. But clinicians already have too large a share of the curriculum and have inadequate hospital material to present because hospitals are so niggardly in the admission of arthritic patients. Orthopedists, with their abundant (if late) material, should therefore accept the duty and welcome the opportunity to "become physicians again." The rheumatic problem should be taught in four ways: by lectures, ward classes, dispensary services, and in the libraries and laboratories. It should be taught, not dogmatically, that is not safe; not by an advocate of any one theory, one may be pleading a bad cause; not by an experimenter, that is too complex for the student. It should be taught by the philosopher with a broad dispassionate viewpoint, by one who above all else avoids the semblance of authority.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR  
OF DOCTOR JOSEPH HERSEY PRATT

## A RARE MANIFESTATION OF GOUT; WIDESPREAD ANKYLOSIS SIMULATING RHEUMATOID ARTHRITIS \*

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ANKYLOSIS may occur in gout. Such ankylosis results because of monosodium urate deposits in the articular tissues. The presence or absence of ankylosis in gout is dependent upon the extent of the urate deposition, its location and the reaction of tissues involved. Ankylosis in gout, however, is rare. When it does occur, it is usually limited to one or two joints, most commonly the small joints of an individual 40 or more years of age, who has been the victim of gout for a long period of years.<sup>1, 2, 3, 4</sup> Most of the references concerning ankylosis in gout are to be found in the writings of the latter half of the last century. All too frequently, it is merely mentioned without describing the pathological changes encountered.<sup>5</sup> Others<sup>6, 7, 8, 9, 10, 11, 12, 13, 14</sup> have described in detail the articular changes resulting from gout. Virchow, as early as 1868, reported a case with complete ankylosis of the terminal phalangeal joint<sup>6</sup> of the great toe. Rarely is widespread ankylosis mentioned, although Litten<sup>15</sup> reported such a case in 1876.

The present case is sufficiently rare to justify a published account because of: (1) The relative youth of the patient; (2) the severity of the gout; (3) the rapidity with which extensive intra-articular changes resulting in widespread ankylosing deformities occurred; and (4) the clinical picture presented by the patient, which when first seen so closely simulated that of an individual with extensive rheumatoid arthritis.

### CASE REPORT

F. N., a white, single, native-born salesman, aged 28 years, was admitted to the medical wards of the Massachusetts General Hospital on December 17, 1934.

*Family History:* There was no known occurrence of gout or arthritis in the patient's relatives. His father, a very obese man, died of a cerebral hemorrhage at the age of 50.

*Past History:* The patient had never been ill except for attacks of measles, chicken pox, mumps and influenza, all without any complications. He had injured the arch of his left foot playing foot-ball some years before the onset of the present illness. This resulted in chipping of one of the small bones of the foot. The bone

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chips were removed in 1925. He had been an individual of extremely good habits and had always been fond of athletics prior to the onset of his present illness. He used neither alcohol nor tobacco.

*Dietary History:* His diet had always been very adequate and well balanced in every regard. His consumption of meat had been normal. He habitually ate liver once a week, but did not ordinarily indulge in foods of high purine content such as brains, kidneys, or sweet-breads. He did not use chocolate or cocoa.

*Present Illness:* In February 1927, at the age of 21, he had his first attack of arthritis. The onset was sudden, without preceding infection or other prodromata such as one frequently observes in rheumatic fever, rheumatoid arthritis, or gonorrheal arthritis. He first noticed severe pain in the left ankle with marked swelling and redness. It was exquisitely tender. There was an associated fever. The right ankle, both knees and both hips were subsequently similarly affected. The arthritis was migratory in nature, tending to clear in one joint (but never completely) before another joint became involved. With subsidence of the swelling, desquamation of the skin overlying the joint occurred. The total duration of the attack was four to five weeks, following which all joint signs and symptoms gradually disappeared. He made a complete recovery without any residua. He had received only symptomatic treatment. A tonsillectomy was done in April 1927, as a preventive against future attacks. Shortly afterward, he was accepted for life insurance.

He remained absolutely symptom-free and apparently well until March 1928, when he suffered another attack of acute arthritis, almost an exact duplicate of that of the year before in that it was of sudden onset, polyarticular and migratory in nature, with associated fever. The same joints were involved. This attack lasted four to five weeks and was again followed by complete recovery. Recovery from this self-limited attack was credited erroneously to the use of several intravenous injections of orthodoxy-benzoic acid.

In 1929, he experienced a similar attack of arthritis again followed by a year of complete freedom. He suffered from a recurrence in 1930 during which he had involvement of the shoulders, elbows, wrists, and fingers for the first time. Injections of "serum" were given without benefit. This attack lasted about the same length of time. He again made a complete recovery, but had two similar attacks of arthritis that same year.

During the next two years, he had two or more such attacks. In 1932, he had dysuria on one occasion following which he passed a small amount of gravel (probably small urate stones). This same year, he noted increasing stiffness of the ankles. Since then, he has had to use a cane or crutches for walking. In 1933, his right wrist and several fingers became stiff. During the 12 months prior to admission he had four attacks of arthritis. These had occurred in November 1933, March 1934, September 1934, and November 1934. The last of these attacks which began three weeks prior to entry caused him to seek further medical aid. The onset had been sudden and was marked by swelling, redness and pain of the ankles, wrists, knees, hips, shoulders, elbows, wrists and fingers. Following each of these last-mentioned episodes, there was increasing stiffness and deformity of the joints involved. The temporomandibular and vertebral joints had never been involved.

The patient had been on a high vitamin-low carbohydrate diet since 1931. This was without effect on the joint symptoms but did result in a 45-pound weight-loss.

#### COMMENTS ON HISTORY

This case history is of importance in that it illustrates many diagnostic points characteristic of the gouty patient and his arthritis as well as some of the unusual features of this particular case.

In attempting to make a correct diagnosis in the case of patients suffering from joint disease, an accurate history is most important. A detailed history will enable one to suspect the correct diagnosis in the majority of the cases. In the remaining few, a complete physical examination and one or two well chosen diagnostic laboratory tests are needed. In an occasional patient, a biopsy may be necessary and most helpful. In rare instances, the passage of time and further observations are indispensable.

In recent years, Hench<sup>16, 17, 18</sup> has tried to make the physicians of this country gout-conscious. In attempting to do so, he has repeatedly stressed as have others<sup>19, 20, 21, 22, 23, 24, 25</sup> in the past the importance of an accurate history. In many instances it alone is sufficient to make a "presumptive" diagnosis.<sup>16</sup> Certainly a suspicious history should always call for a therapeutic test with colchicin. If marked or complete relief always ensues 24 to 72 hours after the onset of colchicin toxicity symptoms, the diagnosis is for practical purposes established. This therapeutic diagnostic test can and should always be carried out even if uric acid determinations are not possible.

In this particular case, the history of recurrent attacks of arthritis, with absolutely complete freedom from joint symptoms between each attack for a period of five years before any permanent joint changes took place, is of itself highly suggestive that the patient had suffered from recurrent gouty arthritis which had finally become chronic.

Recurrent polyarticular, migratory arthritis with associated fever in a young adult would naturally suggest the possibility of recurrent or cyclic rheumatic fever. In this case, however, there were no preceding upper respiratory infections nor any of the other precipitating factors occurring some 7 to 14 days prior to the onset of each attack of arthritis which are so frequently observed in rheumatic fever. None of the associated symptoms of rheumatic fever such as weight loss, skin eruptions, nodules, nose bleeds, tachycardia, precordial pain, etc., was present. Furthermore, with migration of the arthritis, the previously affected joints did not clear so promptly as they regularly do in rheumatic fever. There were no symptoms suggestive of heart disease such as one might rightly expect in a patient who had had so many recurrent attacks of rheumatic fever.

Polyarticular involvement occurs in about 5 per cent of all cases of gout.<sup>16</sup> The younger the individual, the more likely it is to be polyarticular. The polyarticular involvement may be simultaneous or of the migratory type. This form of gout rarely involves the large toe and the attacks are of long duration, usually weeks instead of 7 to 10 days. The fever is more marked and may last weeks. This type is rarely afebrile.<sup>25</sup> It signifies severe gout. It is frequently misdiagnosed rheumatic fever.

A specific infectious arthritis due to the gonococcus is sometimes characterized by recurrences. We have seen one individual who experienced eight such recurrent attacks of arthritis due to a latent focus. In such instances, the story is quite characteristic. There is usually an exacerbation or

recurrence of the genito-urinary symptoms. Particularly is this true in the male. On the same day or a few days later, the patient experiences a chill or chilly sensation followed by fever and migratory aches and pains or a migratory arthritis. This usually subsides after a day or two, leaving one or two joints involved which may show mild or severe inflammatory signs with a corresponding amount of joint pain, etc. Rarely does it remain polyarticular. Although the swelling and other signs of inflammation may be quite severe, they are rarely of the same severity as those seen in gout, where the swelling is more marked, extending further beyond the joint margins than in any other type of arthritis, with the possible exception of certain cases of septic arthritis. Acute gouty arthritis more nearly resembles septic inflammation or extensive cellulitis. There may be an associated lymphangitis. In gouty arthritis, the pain is severe, often described as crushing, worse during the night, letting up in the early morning. The patient protects the joint in every way possible. The overlying skin is red, tense and shiny. The superficial veins are markedly distended. The tenderness is exquisite. As the tenderness subsides, pitting edema is demonstrable. With disappearance of the joint swelling, desquamation of the cuticle and itching follow.

Rheumatoid arthritis in 18 per cent of the cases is characterized by an atypical onset and in 7 per cent may remain atypical for some time, hence the more appropriate name atypical rheumatoid arthritis.<sup>32</sup> This is the group which is all too frequently labelled focal infectious, toxic or non-specific infectious arthritis. The first attack is often acute in onset in an individual who had previously considered himself well. These patients are usually robust and not the asthenic type of individual with evidence of increased vasomotor activity, etc. The attack may or may not be associated with an acute infection or an obvious focus of infection. The joint involvement is usually asymmetrical. It may be polyarticular and migratory. The monarticular form is encountered. Recovery from the first attack may be complete and if so is often ascribed to some therapeutic procedure whereas it truly represents the first self-limited attack of an acute, atypical rheumatoid arthritis followed by apparent recovery. The remission following such an attack is variable. It may be of only a few months' duration, occasionally a year. However, in most instances, it will eventually be followed by a relapse. An individual may have a number of such recurrences and remissions before the disease becomes chronic. As a rule, the remissions are not complete. Frequently there remains certain tell-tale evidence of the previous joint involvement. Rarely if ever will one encounter a case of rheumatoid arthritis with a history similar to that of the patient herein described, of 12 or more acute attacks of arthritis each followed by absolute and complete recovery without residual joint deformity. The marked joint signs, subsequent desquamation, itching, etc., seen in this case are not encountered in atypical rheumatoid arthritis. At

the stage of atypical rheumatoid arthritis where many joints are deformed one will usually find that the joint involvement, particularly of the small joints, is symmetrical.

The typical case of rheumatoid arthritis with preceding constitutional, vasomotor and neurological symptoms, insidious in onset, characterized by symmetrical joint involvement (usually the small joints), should rarely if ever be mistaken for any type of gouty arthritis. In cases with chronic joint deformity with ankylosis due to gout, tophi and other evidence of the disease will be present.

The eliciting of a history of renal colic with the passage of a stone or gravel in an individual suffering from recurrent arthritis should always lead one to suspect gout as the cause of both symptoms.

This patient is of further interest because of the early age (21 years) at the time of onset of his gouty arthritis. The average age of onset has been recorded as 40 years.<sup>16, 25</sup> Pratt states that the youngest case he saw with tophi was a man of 28 years.<sup>25</sup> He further states the disease seldom develops before 20 years of age. One patient observed in this clinic may have had his first attack at nine years of age (it was diagnosed tuberculosis of the hip at that time and he was treated with plaster casts). From the ages of 14 to 19 he had numerous recurring attacks of polyarticular migratory arthritis accompanied by fever. They were always followed by complete recovery. They had always been diagnosed rheumatic fever although he had no endocarditis. When first seen at 19 years, he had a whole blood <sup>26</sup> hyperuricemia of 9.2 mg. per cent. It has continued to run between 12.3 and 14.8 mg. per 100 c.c. serum.<sup>26, 29, 30</sup> He has since developed tophi (age 20 years). Undoubtedly such cases of gout are frequently mislabeled rheumatic fever because of the youth of the patient and the close similarity to rheumatic fever. Such mistaken diagnoses can be avoided if we will become gout-conscious. Repeated careful questioning at each visit will often result in the patient being able to recall earlier attacks which he had failed to mention at the time of his first visit. Such attacks frequently follow slight athletic injury, and are diagnosed sprain or strain, although the severity and duration of symptoms are consistent with a monarticular form of gouty arthritis.

In this instance, there was no family history of gout. There can be little doubt that the frequency with which data indicating heredity are obtained depends upon the degree of thoroughness of the inquiry. Again oft-repeated questioning on subsequent visits plus repeated questioning by the patient of his relatives will result in positive information which had been denied previously.

This patient knew of no precipitating factors. He did not consume excessive quantities of high purine foods and his attacks did not follow gastronomic sprees. We were unable to elicit evidence of attacks following major or minor physical trauma, such as fractures, dislocation, injury,



wearing of tight shoes, after unusual use of a joint, etc.,<sup>17</sup> nor did they follow "physiologic trauma" resulting from protein therapy, severe purging, loss of blood, exposure to cold and wet, etc.<sup>17</sup> He thought worry might have contributed.<sup>17</sup> Such precipitating factors should always be sought. In this case neither of the patient's operations induced an attack.<sup>17</sup> Hench has repeatedly stated "*suspect gout in cases of acute postoperative arthritis, particularly in males.*"<sup>17</sup> This warning is well worth remembering. Operative procedures may also induce an exacerbation of rheumatic fever. In such instances there is the usual latent period of seven to 14 days between the operation and the onset of the arthritis. Although rheumatoid arthritis is frequently followed by immediate improvement, usually shortlived, following surgical procedures, it is occasionally activated or increased in severity. This is probably an effect of the ether anesthesia and not due to the removal of an obvious focus of infection.

The prodromata preceding an attack of gouty arthritis are variable. Some state that they feel their best before each attack, others complain of nausea, indigestion, melancholia, polyuria, nocturia, stiffness, aching, etc.



FIG. 1. This schematic chart depicts the frequency of the recurrent attacks of acute disabling gouty arthritis experienced by this patient. It will be noted that one such attack occurred each spring for the first four years. They then increased in frequency. Residual joint changes were present after the first five years. (Each peak represents an attack. The solid black area from 1932 on indicates the approximate disability present.)

From figure 1 it will be noted that the attacks first came once a year, usually in March or April. More attacks occur between April and June than at any other time of the year.<sup>17</sup> After four years, the frequency of attacks increased to two to four per year and at the end of five years, the patient had residual joint deformity. The time between the first and second attacks is variable. It may be months or years. In 100 cases, the patients averaged one attack every 1.7 years.<sup>16</sup> The average for each attack was 13 days. The interval between attacks becomes less with each subsequent attack until chronic joint deformity becomes evident. To have as marked crippling at the end of five years as was noted in this case is most unusual. Such marked crippling is more apt to be seen in the polyarticular form and represents the more severe type of gout. Only 2 per cent of cases of gout are chronic from the onset.<sup>16</sup>

An important thing to remember is that gouty patients feel unusually well between their attacks; as one patient stated, "my arthritis is almost

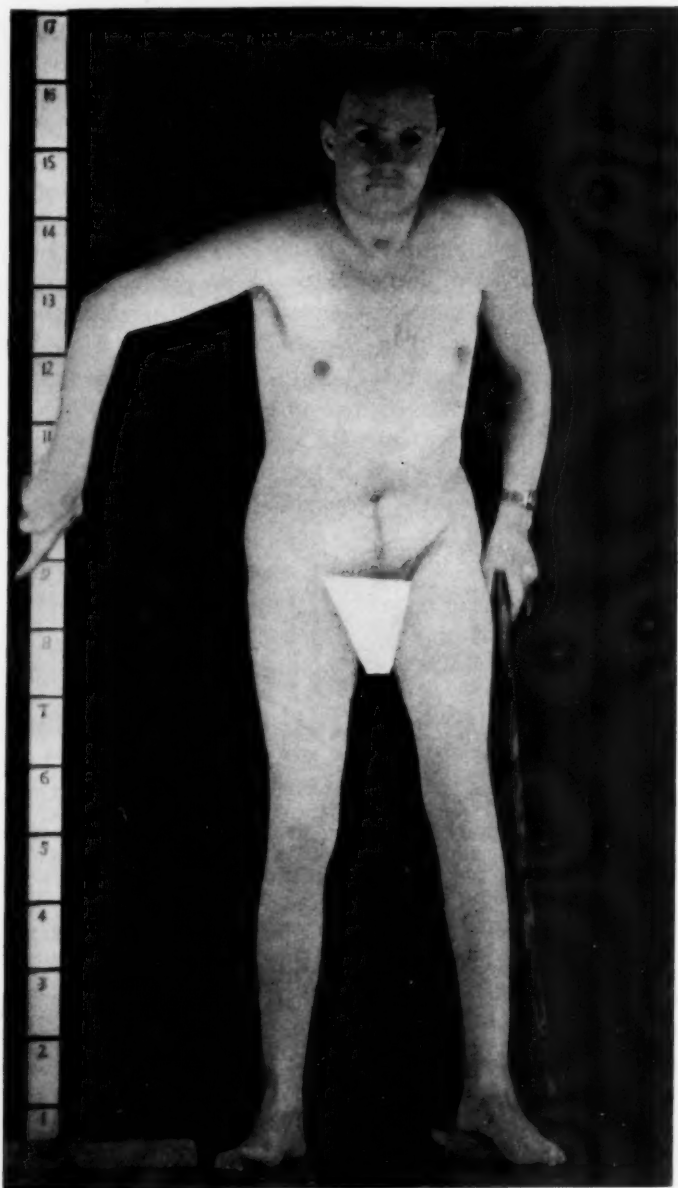


FIG. 2. This anterior view of the patient shows the degree of disability present at the time of entry. He had to support himself because of the flexion contractures of the knees and the ankylosed ankles. The equinus deformity of the left foot is apparent. The manner in which he grasped the measuring stick and cane serves to illustrate the deformities of the elbows, wrists and fingers.

unbearable, yet between attacks, I am as fit as a fiddle." The attacks of arthritis are self-limited. Many of the so-called specific therapeutic measures for rheumatoid arthritis such as vaccines, sera, colloidal injections, removal of infected foci, colonic irrigations, endocrine therapy, etc., are prescribed and erroneously given credit for curing an attack of rheumatoid arthritis, whereas the patient was suffering from a self-limited attack of gouty arthritis.

#### PHYSICAL EXAMINATION

The patient was examined on December 17, 1934. He was a fairly well developed, moderately obese young man (figure 2). The skin of the hands was cool and moist. There were erythematous patches on the skin of the cheeks and forehead, with scaling of the forehead. Brownish pigmentation of the skin was present over the dorsum of the hands and feet, the fingers, and the toes. Over the interphalangeal joints of the fingers, the skin was dry and scaling. The eyes, ears, nose, throat and sinuses were not remarkable. The tonsils were out. The teeth and gums were in good condition. The lungs were normal to percussion and auscultation. The heart was normal in size, the sounds of good quality, the rhythm regular, and there were no murmurs. The systolic blood pressure was 124 millimeters of mercury, the diastolic 90. Examination of the abdomen revealed no abnormality. The knee jerks were difficult to obtain, other reflexes could not be tested because of the extensive joint involvement. The prostate was normal. Prostatic massage yielded no secretion.

There was a lesion resembling a tophus on the left ear. Nodular enlargement of the left olecranon bursa was present. There was a suggestion of beginning subcutaneous tophi over the terminal phalangeal joint of the right index finger (figure 3A).



FIG. 3A. Photograph of the hands, showing the marked flexion and hyperextension type of deformity present in the fingers. One further notes swelling of the second and third left metacarpophalangeal joints. The tophi present in the right index finger at the time of entry are readily seen (figure 3A). These became more marked (figure 3B) and finally discharged monosodium urates (figure 3C).

*Examination of the Joints:* All the finger joints were affected. There was a slight flexion deformity of the terminal phalanges of the second, third, fourth and fifth fingers of both hands. The interphalangeal joints of the right second, third and fourth fingers were ankylosed in a position of  $10^{\circ}$  hyperextension. The left second, third and fourth fingers were similarly involved (figure 3A). There was slight flexion of the left fifth interphalangeal joint. Ankylosis, with slight flexion deformity, and subluxation of the interphalangeal joint of the left thumb were noted.

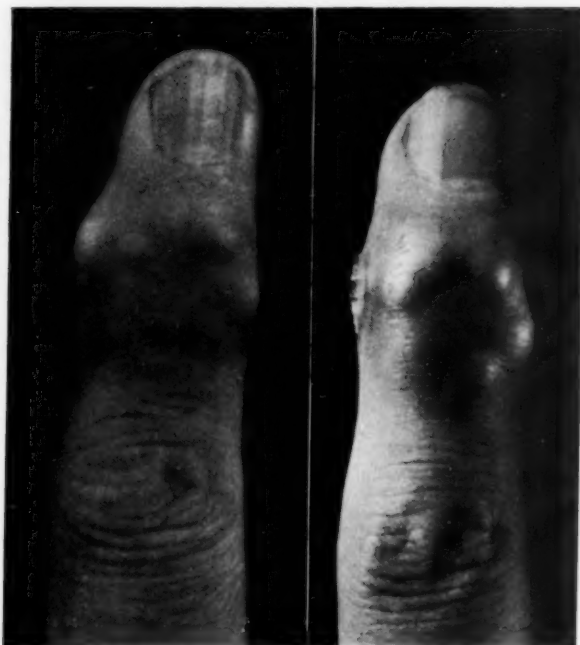


Fig. 3 B.

Fig. 3 C.

There was tenderness and limitation of motion of the metacarpophalangeal joints on both sides, more marked on the left. The grip of the right hand was poor, and there was inability to flex the fingers. The grip of the left hand was fair. The skin over the finger tips was atrophic. There was marked atrophy of the interosseous muscles of both hands. Lateral pressure applied to the palms proved to be painful on both sides. The right wrist was completely ankylosed in  $35^{\circ}$  of flexion. The elbows could be fully flexed, but they lacked 10 to  $15^{\circ}$  of extension. There was no limitation of motion in the shoulders, although pain resulted with extremes of motion. The dorsal and lumbar spine showed very slight limitation of motion in all directions. The cervical spine was normal. The sacro-iliac joints were normal. The temporo-mandibular and sternoclavicular joints were uninvolved. There was about 40 per cent limitation of motion in all directions in both hips. The right knee was limited in motion. It lacked  $30^{\circ}$  of full extension. Flexion was possible to an angle of  $60^{\circ}$ . The left knee lacked  $15^{\circ}$  of full extension, and could be flexed only to about  $60^{\circ}$ . The quadriceps pouch insertion was thickened on both sides. Grating was palpable on motion of both knees. The patellae were not movable. Synovial thickening and irregularities of the articular margins of the knees could be detected on palpation. The left ankle was nearly completely fused in  $10^{\circ}$  of extension, only a jog of motion

being present in any direction. Motions of the right ankle were markedly limited. Both feet were almost completely fixed. Lateral pressure applied to the metatarsophalangeal joints was painful. Only slight flexion or extension of the toes was possible. All of the toes deviated laterally.

#### COMMENTS ON PHYSICAL EXAMINATION

The admission diagnosis was chronic infectious or rheumatoid arthritis. The diagnosis of rheumatoid arthritis after complete physical examination seemed justified because the patient exhibited many of the features commonly encountered in this disease, increased vasomotor activity, brownish pigmentation of the skin of the hands and feet, widespread joint involvement with extreme ankylosis (figure 2), the characteristic appearance of the hands and fingers (figure 3A) (shiny atrophic skin with hyperextension and flexion type of deformities of the fingers) and supposed rheumatic nodules in the olecranon bursa (figure 4). However, subsequent examinations revealed a suggestive tophus in the left ear (figure 5). Dissolving



FIG. 4. Photograph of the left olecranon bursa. It contained numerous, hard, nodular tophi.

the material obtained from this lesion with hydrochloric acid revealed uric acid crystals. The material gave a positive murexid test. This finding led to the suspicion that the olecranon bursa and the swelling over the terminal phalangeal joint were also tophi. Subsequent examination of material obtained from them confirmed this suspicion.



If one suspects gout, he should make a diligent search for tophi. Subcutaneous tophi are most commonly found in the helix of the ear. They are white, cream-colored, or yellow, varying in size from that of a pin head to a pea. Except in severe gout they rarely appear before 10 years.<sup>16</sup>



FIG. 5. Tophus seen in the right ear.

They are pathognomonic of gout but should never be considered such until the monosodium urate crystals have been demonstrated or until a positive murexid test is obtained. They are also found in the cartilage of the nose, along the tendons of fingers, hands, toes and feet and the patellar tendons, patellar and olecranon bursae. The last-mentioned should not be confused with the bursal and subcutaneous nodules of rheumatoid arthritis (figure 6) or rheumatic fever. When the skin overlying a tophus breaks down, a mixture of chalk and water is discharged. The old discharging tophi contain hard chalk-like material.

*Although gout commonly affects the big toe, it does so in only 54 per cent of the cases in the initial attack.<sup>16</sup>* As can be seen from this case, almost any joint may be involved. This is true whether the arthritis is mono- or polyarticular. Evidently the spine and sacro-iliac joints are rarely involved. Joint effusions do occur. The temporomandibular and sternoclavicular joints, relatively frequently involved in rheumatoid arthritis, are rarely affected in gout.

If the initial examiner had been gout-minded, he would not have overlooked the ear tophus and would have correctly interpreted the olecranon bursitis.

## INTERPRETATION OF ROENTGENOGRAMS

*December 1934:* Roentgenological examination showed extensive changes in most of the joints examined. The joint spaces of the middle phalangeal joints of all the fingers were narrowed. Irregularity of the articular surfaces was present in the



FIG. 6. Rheumatic nodules in the olecranon bursa of an individual suffering from rheumatoid arthritis. The nodules had been present for one year.

middle phalangeal joints of the little fingers, the left being fused (figure 7). Similar changes were seen in some of the terminal phalangeal joints of both hands (figure 7). There was gross destruction and deformity with partial dislocation of the first and second left metacarpophalangeal joints. The right wrist showed irregularity of the joint surfaces with narrowing of the joint spaces. The changes in the left wrist were slight. There was narrowing of the joint space of the elbows. The film of the pelvis showed irregularity and indistinctness of the outline of the left sacro-iliac joint. There were marked hypertrophic changes about the right knee (figure 8). An anteroposterior view of the left knee showed narrowing of the joint space (figure 8) (due in part to the flexion deformity). There were small irregular areas of decreased density in the central portion of the articular surfaces of the femur and the corresponding area of the tibia. The feet and ankles showed changes similar to those seen in the wrist and finger joints (figures 9 and 10). There was calcification of pelvic and leg vessels.

*Diagnosis:* All of these changes were thought to be consistent with infectious arthritis. The hypertrophic changes in the knees were interpreted as being secondary to a previous infectious arthritis.

*March 1936, 16 months later:* At this time the joint changes mentioned above were found to be more extensive. The narrowing of the joint spaces had increased. There was more new bone formation and the deformity of joint surfaces was more



FIG. 7. Roentgenograms of the hands, showing decalcification of the bones of the fingers in the region of the joints. Narrowing of many of the phalangeal joint spaces is present. Similar changes are present in the terminal phalangeal joints. Irregularity of the articular surfaces of the middle phalangeal joints of the little fingers is seen, the left being fused. The punched-out area in the distal end of the phalanx of the right second finger appeared in one year's time. There is marked destruction of the metacarpophalangeal joints of the first and second left fingers. The distal end of the phalanx of the right third finger is amputated. The right wrist shows irregularity of the joint surfaces and narrowing of the joint spaces.

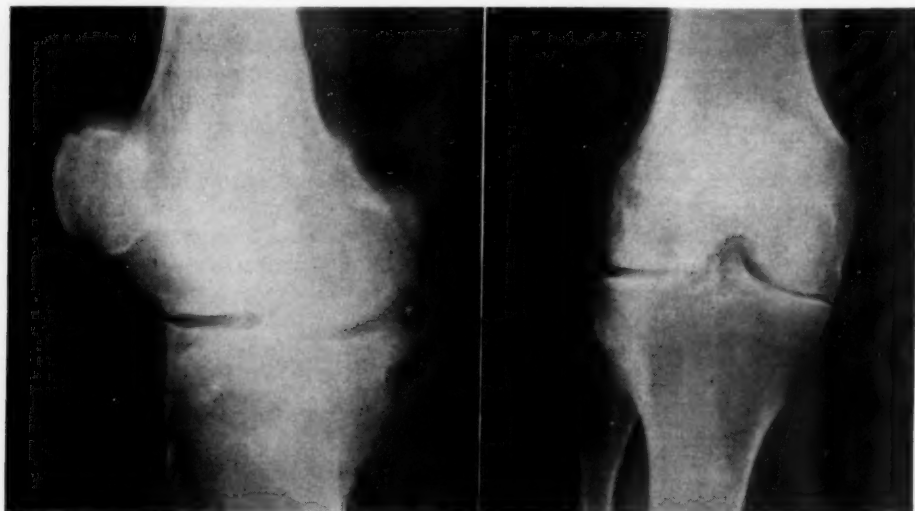


FIG. 8. Anteroposterior and lateral views of the right knee, showing some decalcification of the bones, narrowing of the joint space and marked marginal overgrowth of the femur and tibia.

marked. The distal extremity of the right third finger had been amputated (surgical) (figure 7). There was partial fusion of some of the tarsal joints. There was obvious destruction and deformity of both the first as well as the second left metatarsophalangeal joints. Localized punched-out areas were present in the bones of



FIG. 9. Anteroposterior roentgenogram of the feet demonstrating decalcification of the ends of the phalanges and joint narrowing. Areas of destruction and punched-out areas are present in the bones of both the first metatarsophalangeal joints.

the distal extremity of the middle phalanx of the right index finger, and adjacent to both first metatarsophalangeal joints (figures 7 and 9), as well as at the superior margins of the left os calcis. There were similar but less marked areas of destruction in the metacarpophalangeal joints of the left first and second fingers, the right fifth finger, and the proximal phalangeal joint of the fifth finger. Bone atrophy was present to a marked degree in the bones of the ankles, moderate in the hands and feet. There was some soft tissue thickening about the joints showing bone destruction. The disease was symmetrical in character, several of the phalangeal, metacarpophalangeal and metatarsophalangeal joints being normal. There was calcification of the blood vessels in the lower extremities.

Roentgen-ray examination of the teeth showed unerupted upper third molars, and several malposed teeth. Roentgen-ray study of the sinuses, lungs, heart, abdomen, colon, kidneys and gall-bladder revealed no abnormalities.

#### COMMENT ON ROENTGEN-RAY INTERPRETATION

The roentgen-ray findings suggestive of gout are punched-out areas, usually 5 mm. or greater in diameter, most commonly located in the subchondral bone of the base or head of the phalanges of the hands and feet. Such changes may be late in appearing. In Hench's series,<sup>16</sup> 19 cases with tophi and hyperuricemia had had their disease 28 years or longer and yet

no roentgenographic changes were present. Marginal hypertrophy of the bones involved is a frequent finding. These subchondral punched-out areas are not to be confused with those seen in hypertrophic arthritis and rheu-



FIG. 10. Lateral view of the left foot showing the marked decalcification, destruction of joint surfaces, and ankyloses.

matoid arthritis. In the latter, generalized decalcification is usually present. Occasionally similar findings are encountered in the case of the gummata of syphilis, leprosy and yaws as well as in tuberculosis and sarcoid.

In this case the roentgen-ray findings were most misleading because of the widespread involvement, marked destruction and deformity, decalcification of the bones of the involved joints and obvious ankylosis. These changes resemble more nearly those of a specific infectious arthritis or rheumatoid arthritis. Marked hypertrophic changes at so early an age are most commonly secondary to a preëxisting rheumatoid or specific infectious arthritis. These joint diseases, we should bear in mind, do cause sufficient joint damage so that subsequent wear and tear changes in these altered structures lead to premature development of well marked hyper-



trophic changes. Without the clinical history, the roentgenologist could not be expected to make the correct diagnosis.

The finding of arteriosclerosis at the age of 28 bears out the finding of others<sup>24, 25</sup> that arteriosclerosis appears at an earlier age in gouty subjects.

#### LABORATORY DATA

Hemoglobin (Tallquist) 90 per cent. Red blood cell count 4,560,000; white blood cell count 15,000. The differential leukocyte count showed 78 per cent polymorphonuclear neutrophils, 16 per cent lymphocytes and 6 per cent large mononuclear cells. The maximal urine concentration observed was 1.012. The urine specimens contained neither albumin, sugar, nor diacetic acid. The sediments were negative except for occasional leukocytes and hyaline casts. Stool examinations were negative. The Hinton test was negative. A gonococcus complement fixation test was negative. The sedimentation rate (Ernstene-Rourke method<sup>47</sup>) was 0.89 to 1.3 mm. per minute, 0.35 mm. per minute being the upper limit of normal. The serum non-protein nitrogen ranged between 20 and 27 mg. per 100 c.c. The fasting whole blood uric acid was 5.2 to 6.5 mg. per 100 c.c. (Folin method<sup>26</sup>) for which the upper limit of normal is 5.0. A fractional intravenous phenolsulphonephthalein renal function test showed a 13 per cent excretion in the first 15 minutes, 10 per cent in the second 15-minute period and 23 per cent in the second half-hour, a total of 60 per cent. This, according to Chapman's<sup>27</sup> data, indicates definite kidney impairment. The bromsulphthalein liver function test was normal. The blood cholesterol values were always normal. Fasting gastric analysis revealed no free hydrochloric acid. After histamine injection it reached 15. The arterial-venous sugar tolerance curve after the ingestion of 100 grams of glucose was as follows:

	Arterial	Venous
Fasting .....	96	97
One-half hour .....	166	153
One and one-half hours .....	242	218
Three hours .....	159	146
Four hours .....	100	97

No glycosuria was observed during the test.

#### COMMENT ON LABORATORY DATA

A mild to moderate leukocytosis is always observed in patients with gouty arthritis. Evidence of mild renal impairment such as found in this case is not an infrequent finding in gouty patients.<sup>16, 25, 28</sup> Many of them die of uremia.<sup>28</sup> Therefore, one should remember the statement "chronic arthritis associated with distinct renal impairment suggests gout until proved otherwise."<sup>16</sup> Urinary gravel and renal stones were present in 12 of 100 cases.<sup>16</sup> Achlorhydria appears to be no more frequent in gouty patients than in other individuals. An abnormal peak type of sugar tolerance curve such as seen in this patient has been observed in other gouty patients as well as in patients with rheumatoid arthritis.<sup>32</sup> That this is of no diagnostic significance is shown by the fact that in other individuals with the same types of joint disease normal sugar tolerance curves are observed. We have frequently observed an increased sedimentation rate in gout.<sup>32</sup> In several instances the rates have been as high as 2.0 mm. per minute. Such increases

are not necessarily related to alterations in the serum proteins because in several instances they have been noted in subjects having normal serum albumin and globulin values.<sup>32</sup>

#### SUBSEQUENT COURSE

During his hospital stay, the patient experienced numerous attacks of arthritis, varying considerably in severity (figure 1). Some were extremely mild (+), others quite disabling and extremely painful (++++). One such attack lasted two weeks, involved most of his joints and was accompanied by a temperature of 103.5° F. (rectally) at times. Such attacks always responded very promptly to colchicin (grains 1/120 every 1½ hours), provided it was given until toxic symptoms (nausea, vomiting and diarrhea) appeared. Eight such tablets were usually necessary. The course of his gout and of the hyperuricemia was not materially influenced by a low purine diet over a period of three months.<sup>29</sup> The severity and frequency of his attacks while on a low purine diet did bear a relation to the urinary uric acid concentration (table 1).

TABLE I

Showing the Relationship Between the Uric Acid Excretion and the Attacks of Arthritis				
Date	Urine Volume c.c.	Uric Acid Excretion mg.	Concentration of Uric Acid	Symptoms
			mg. per 100 c.c. Urine	
1/28/35	1540	580	37.6	0
1/29/35	1380	670	48.5	0
1/30/35	1450	1040	71.7	+
1/31/35	1730	1250	72.2	++
2/1/35	1920	2180	113.5	++
2/2/35	1680	2180	129.7	+++
2/3/35	1510	1890	125.0	+++
2/4/35	1730	1730	100.0	++
2/5/35	1960	1380	70.4	+
2/6/35	1890	1270	67.1	+
2/7/35	2130	1100	51.1	++
2/8/35	1840	1220	66.3	++
2/9/35	1790	1040	58.1	+
2/10/35	1630	670	41.1	+
2/11/35	1750	980	56.0	+
2/12/35	1910	750	39.2	+
2/13/35	1760	810	46.0	0
2/14/35	1750	880	50.2	0
2/15/35	2070	940	45.4	0
2/16/35	1760	990	56.2	0
2/17/35	2170	1140	52.5	0
2/18/35	1770	850	48.0	0
2/19/35	2000	830	41.5	0
2/20/35	1810	980	54.1	0

The patient was on a low purine diet during this period. We are indebted to Drs. Jacobson and Talbott of this clinic who made these determinations.

His treatment during these first two hospital stays was directed toward correction of the deformities. This was attempted by means of various types of splints and casts and operative procedures\* in conjunction with exercises.

The olecranon bursa was subsequently removed (specimen I). It was filled with white, chalky material. Typical monosodium urate crystals giving a positive murexid

\*The biopsies and operations were performed by Drs. F. A. Simeone, G. W. VanGorder and Sumner Roberts.

test were readily demonstrated. In order to determine with absolute certainty that the ankylosis was due to gout and not to a co-existing rheumatoid arthritis, the patient consented to a biopsy of his left ankle and foot. Biopsy specimens were removed from the ankle (specimens II and III) and the scaphoid-cuneiform joints (specimen IV). It is interesting in connection with this point that the patient's serum did give positive agglutination tests for hemolytic streptococci (Strains NY<sub>s</sub> and C<sub>17</sub>) on several occasions. In one instance the titer was 1/1280. On other occasions, however, such agglutination tests were negative.

At a later date the patient requested amputation of the head of the proximal phalanx of the third finger in order to correct the hyperextension deformity as well as to give him a movable joint (specimen V). In order to overcome the flexion deformity of the right knee, a capsuloplasty was done. The tissue removed at the time of this operation represents specimens VI and VII. All the biopsy specimens are described in detail under pathological findings.

This patient has been under constant observation since his initial hospital entry. Studies pertaining to his hyperuricemia have been reported in this same volume (Case 2) by Jacobson.<sup>29</sup> Further detailed metabolic studies, similar to those previously reported<sup>30</sup> have been made by Dr. J. H. Talbott and will be reported in future publications.

#### COMMENTS ON SUBSEQUENT COURSE

Except for one serum uric acid value of 5.2 mg. per 100 c.c. (following a salyrgan diuresis), this patient has always exhibited a fasting hyperuricemia of 6 or more mg. per 100 c.c. of serum.<sup>29</sup> During as short a period as seven weeks, Jacobson made 33 fasting serum uric acid determinations on this patient.<sup>29</sup> These 33 values varied between 7.4 and 14.5 mg. per 100 c.c. The patient received no treatment during this period. Jacobson also presents the serum uric acid variations encountered during a period when the patient was having attacks of gouty arthritis as compared with an attack-free period. In each instance the patient was on a low purine diet without other therapy. Of 13 determinations made during a period with arthritis, the fasting serum uric acid varied from 10.5 to 14.5 mg. per 100 c.c. with a mean value of  $12.4 \pm .20$ , whereas during the arthritis-free period, 20 determinations were found to vary from 7.4 to 13.6 with a mean value of  $12.1 \pm .30$ .

Of the 177 fasting serum uric acid determinations made on 21 untreated gouty subjects Jacobson found that 174 or 98 per cent exceeded a value of 6 mg. per 100 c.c. Ninety-four per cent or 167 exceeded a value of 7 mg. per 100 c.c. Our experience with a larger series of gouty subjects<sup>32</sup> on whom less frequent determinations have been made is the same, namely, that the fasting serum uric acid value of untreated gouty patients whether free of arthritis or not has always been 6 mg. per 100 c.c. or over. From these data, it would appear that a hyperuricemia is practically if not always present in untreated presumptive or tophaceous gout. There may well be exceptions to this rule but if so they have not been encountered in this clinic.<sup>29, 30, 31, 32</sup> Jacobson was unable to prove that the same change in the serum uric acid always preceded the attack of the arthritis. From his data it would seem that it might vary considerably from individual to individual

and from attack to attack. In some instances it was unchanged, in others decreased or elevated. Various workers report lowering of the uric acid following treatment. It is hazardous to draw such conclusions unless the possible variations in any one subject have been well established by daily determinations over a period of seven to ten days prior to the institution of said therapy. If such control studies are not made on each patient treated, one may interpret lowering of the serum uric acid as having resulted from the treatment, whereas it may represent nothing more than the naturally occurring variations of that particular individual. Until such well controlled metabolic studies with various types of treatment have been made, we will not know the correct answer to such questions.

We are of the opinion that the requirements for uric acid determinations laid down by Talbott and Jacobson<sup>29, 30, 31</sup> must be adhered to if we are to obtain comparable values giving the smallest possible variations. These are: Drawing of the fasting blood under oil, transferring it to a tube under oil, allowing it to clot, centrifuging and transferring the necessary amount of overlying serum to an Erlenmeyer flask. One can employ either the Folin<sup>36</sup> or the Benedict<sup>37</sup> method.

From table 1, it will be seen that the concentration of uric acid per 100 c.c. of urine while on a low purine diet was always greatest at the time of arthritic symptoms. A normal individual rarely excretes more than 0.6 gram per day.<sup>24, 25</sup> The average daily excretion for 20 gouty patients was 0.25 gram.<sup>24, 25</sup> As Pratt points out "probably 5 per cent of gouty patients have a uric acid excretion which is either a high normal or supernormal."<sup>25</sup> In this instance, a high uric acid excretion was possible even though slight renal impairment was present.

The treatment for the acute attacks of arthritis in this case has rarely been other than colchicin. This drug is practically a specific for acute gouty arthritis. It should be administered in pill form, grains 1/120 every one or two hours until nausea, vomiting, and diarrhea appear. It is then discontinued. Freedom from pain and subsidence of swelling occur within 24 to 72 hours. The diarrhea is usually sufficiently severe to require treatment with paregoric or bismuth subnitrate. Once the patient has established the amount necessary to produce such symptoms, he can reduce the total dose by 1 or 2 pills and still accomplish the desired effect. Occasionally opiates are required, though rarely if colchicin is administered as soon as the first warning symptoms appear. The patient should always carry his colchicin with him. Besides such therapy for the acute arthritis, we advise avoidance of the few high purine-containing foods and known precipitating factors, a high fluid intake and large doses of aspirin 60 to 80 grains four days out of every week. We never employ cinchophen because of the risk of inducing acute yellow atrophy and the fact that the pill form of colchicin is equally if not more efficacious. We are doubtful if this or any other regime of therapy materially affects the course of the disease. Again, one

must proceed with caution and have conditions extremely well controlled before concluding that the frequency, duration and severity of the arthritic attacks have been materially influenced. We must bear in mind the natural course of the disease, the natural interval of time between attacks and that the attack of arthritis is usually self-limited.

The necessity of employing certain medical orthopedic measures, such as some physiotherapeutic procedures, aspiration of effusions, immobilization in casts, correction of deformities by casts and operations, etc., must be borne in mind.

#### PATHOLOGICAL EXAMINATION

Specimen I. (The olecranon bursa.) It measured 2 by  $1\frac{1}{2}$  by 1 cm. A soft, grayish-white, chalky material was easily expressed from freshly made sections. Microscopic examination revealed numerous, varying sized deposits of a non-cellular, lightly staining, foreign material. Under high power magnification this material was seen to consist of masses of needle shaped crystals. Many of these deposits were partially surrounded by foreign body giant cells, mononuclear leukocytes, lymphocytes, and plasma cells. Focal areas of heavy mononuclear inflammatory cell infiltration were also observed.



FIG. 11. Photomicrograph of low magnification ( $\times 10$ ) showing fibrous ankylosis of the astragalotibial joint. The cancellous bone of the astragalus is shown in the upper portion of the photograph. Small strips of eroded articular cartilage adjacent to the astragalus represent the only remaining articular cartilage. Note the numerous light areas (arrows) in the connective tissue that have replaced the joint space. These are monosodium urate crystals. They are surrounded by zones of marked chronic inflammation. Celloidin section stained with hematoxylin and eosin.

Specimen II. (Biopsy of astragalotibial joint.) The specimen measured  $1\frac{1}{2}$  cm. in length and 7 mm. in width. Near one margin of the specimen was a plate of



cartilage, representing the astragalotibial articulation. This measured 3 mm. in thickness and was bounded on either side by cancellous bone. Sections from this specimen showed a large area of cancellous bone from the astragalus. The overlying articular cartilage was covered by a thick layer of dense, moderately vascular, heavily infiltrated fibrous tissue (pannus). Extremely numerous urate deposits were present throughout this layer of pannus. Most of the urate deposits were of small size. They were surrounded by a heavy infiltration of mononuclear phagocytes and foreign body giant cells. Occasional larger deposits were observed. Numerous focal areas of dense lymphoid cell infiltration were present. The intervening connective tissue was moderately heavily infiltrated with lymphocytes, mononuclear leukocytes and polymorphonuclear leukocytes.

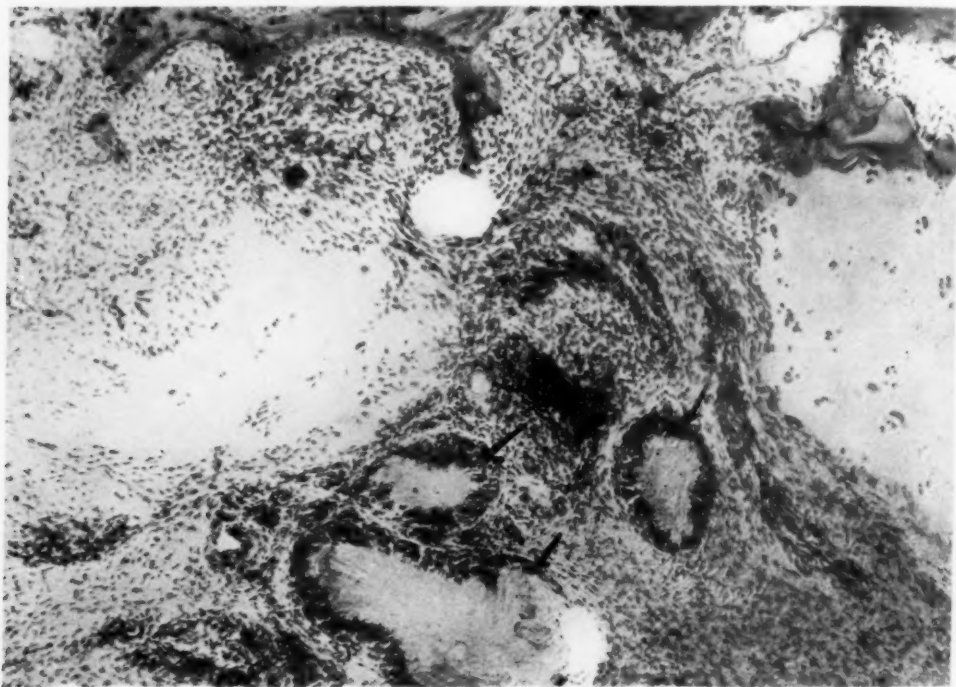


FIG. 12. A higher power photomicrograph of area outlined in the above photomicrograph. Note the invasion of articular cartilage by fibrous tissue, the areas of sodium urate deposits (arrows) and the adjacent inflammatory cell infiltration of the tissues. Magnification  $\times 100$ .

The underlying cartilage contained numerous small pits. These represented areas of destruction due to the invasion by the very cellular, vascular pannus tissue. In most instances such depressions contained one or more masses of urate deposits. Additional evidence of injury to the articular cartilage was exhibited by the absence or diminution in the number of cartilage cells in the more superficial areas as well as by irregularities in the matrix of the cartilage surface directly beneath the pannus. In a few areas complete destruction of the cartilage had resulted and the heavily infiltrated vascular connective tissue had penetrated the calcified zone of cartilage and extended into the subchondral bone spaces of the astragalus.

Specimen III. (Biopsy of astragalotibial articulation.) In this specimen, the astragalotibial joint space was replaced by a 3.5 mm. band of fibrous tissue. The

entire specimen measured 1.2 by 1 cm. The histological changes observed were very similar to those seen in specimen II, except that both bones entering into the articulation were shown. These were firmly united by a dense, moderately vascular fibrous tissue (fibrous ankylosis). The subchondral bone spaces were extensively invaded by connective tissue, infiltrated with numerous inflammatory cells. The remaining cartilage consisted of small irregular fragments which were completely surrounded by fibrous tissue (pannus). Urate deposits were very numerous throughout the fibrous tissue which had replaced the joint space (figures 11 and 12).

Specimen IV. (Biopsy of the scaphoid-cuneiform joint.) It measured  $1\frac{1}{2}$  by 0.7 cm. in its greatest dimensions. It included one peripheral margin of the scaphoid and cuneiform articulation. One section through this articulation showed no abnormalities in the subchondral bone except at the extreme margin of the joint. In this region, urate deposits were observed in a few of the marrow spaces of the bone on either side of the joint. Such urate deposits were surrounded by heavy inflammatory cell infiltration including foreign body giant cells. One also noted considerable vascular fibrous tissue replacement of the bone marrow tissue wherever



FIG. 13. An isolated urate deposit deep in the cancellous bone of the finger illustrated in the following photomicrograph. Examination of serial sections proved that this and other deposits of sodium urate were entirely within cancellous spaces of the subchondral bone. Celloidin section—hematoxylin and eosin stain. Magnification  $\times 100$ .

urates had been deposited. The overlying cartilage in these areas had been completely destroyed, suggesting that the invading urate-containing fibrous tissue had come from the joint space. However, we could not be certain because the joint capsule in this region was likewise the site of urate deposits and marked proliferation.

Elsewhere in the section the articular cartilage was thinned out and very irregular in contour. Urate deposits unaccompanied by pannus were observed on both articular

surfaces. Extensive degeneration of the remaining cartilage was present as shown by the absence of many of the cartilage cells and marked fibrillation of the remaining matrix. No appreciable amount of pannus was found on the remaining articular surfaces.

Specimen V. This consisted of the head of the proximal phalanx of the right third finger and several small fragments of the articular capsules. The articular cartilage was gray and non-glistening, measuring approximately 1 mm. in width. Its surface was uneven because of numerous pits. The head of this proximal phalanx was divided in the mid-line. Serial sections were cut from each block towards the periphery of the specimen. This was done in order to demonstrate whether the deposition of urates in the subchondral bone spaces was primary or the result of urate-containing pannus penetrating through the articular cartilage. Because of the extensive nature of the lesions, it was impossible to answer this point with absolute certainty. However, the occurrence of isolated urate deposits (figure 13), deep in the subchondral bone spaces, and the occurrence of small deposits on the surface of the articular cartilage was interpreted as strong evidence that the destructive lesions about the joints can be due to either. This is what one would expect in a metabolic disease. The uneven articular cartilage surface was again due to superficial urate deposits and the accompanying degeneration of the cartilage cells and matrix. In addition, one noted large circular defects extending through the entire thickness of articular cartilage into the underlying subchondral bone (figure 14).

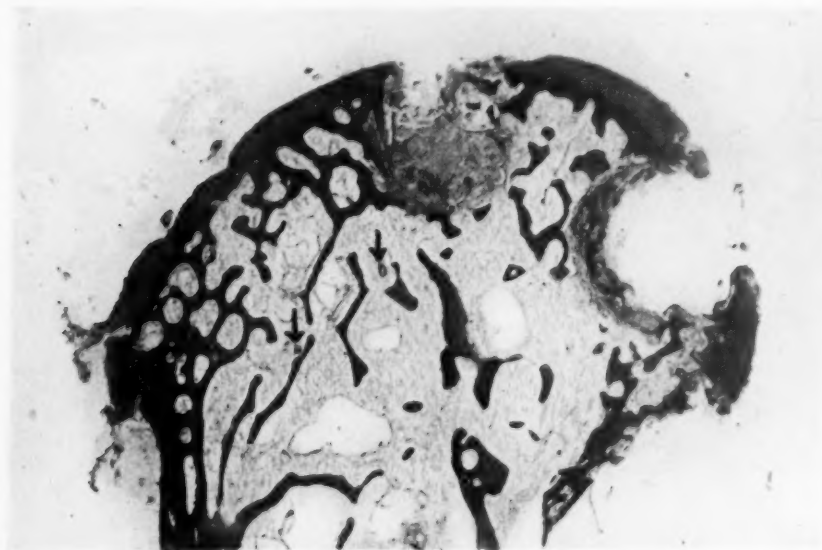


FIG. 14. Photomicrograph ( $\times 10$ ) showing the articular end of the proximal phalanx of the third left finger. The free surface of the articular cartilage is frayed and uneven. Cartilaginous and bony overgrowth (lipping) is present at the articular margins. Two large circular defects (punched-out areas) are present in the articular cartilage and subchondral bone. These lesions are lined by fibrous tissue which is infiltrated with large numbers of inflammatory cells and studded with numerous masses of sodium urate crystals. Note the isolated urate deposits in the bone marrow (arrows). Celloidin section stained with hematoxylin and eosin.

These defects were filled with large masses of urate crystals, which were surrounded by heavily infiltrated sheaths of connective tissue. The adjacent bone trabeculae showed evidence of moderate lacunar absorption. In some areas the histological

appearances suggested that following extensive undermining of the calcified zone of cartilage, collapse of the overlying articular cartilage had taken place (figure 14). Cartilaginous and bony overgrowth was present at the articular margins.

Specimen VI. It consisted of a piece of capsular tissue from the knee joint. Microscopic examination revealed that it was studded with large and small foci of urate crystals. Such urate collections were surrounded by a cellular zone containing numerous mononuclear cells having the appearance of epithelioid cells. Lymphocytes, eosinophiles and occasional giant cells were also present. In the areas free of urate deposits the tissues consisted of extremely dense contracted fibrous tissue.

Specimen VII. A small strip of articular cartilage from the posterior aspect of the femoral condyle. It was greatly reduced in thickness. Its surface was extremely uneven. The perichondrial margin was covered by a thick layer of fibrous tissue. The cartilage itself contained numerous small urate foci. The irregular surface pits and depressions were covered by urate deposits. The cartilage matrix was fibrillated, the cells unevenly arranged, in many regions being grouped in clumps.

#### COMMENT ON PATHOLOGICAL EXAMINATIONS

The evidence that gout is a metabolic disease is quite convincing. The fact that one can, with persistence, obtain a positive family history in a high percentage of cases is of itself extremely good evidence that it is probably an inborn disease of metabolism. Further studies on the children of gouty patients will give further evidence in this direction. Its occurrence in women is rare.<sup>3, 5, 9, 16, 24, 25</sup> Irrespective of the various metabolic alterations observed in such patients, one fact remains, namely, that the pathological changes observed in gout are secondary to the deposition of monosodium urate. Urate tophi are the only known specific lesions of gout. This is true of the cutaneous, articular and visceral structures, and possibly the vascular sclerosis as well, because such sclerotic lesions are readily demonstrated in the region of urate deposits, and accompanying the heavily infiltrated vascular fibrous tissue about them. The factors which govern the diffusion of urates into the various tissues are as yet unknown. Once they become extravascular, they serve as foreign body irritants in consequence of which proliferation occurs. We do not know the factors responsible for the more frequent deposition of urates in the articular and subcutaneous tissues. It is true that visceral tophi have been observed, but many of the reported instances can hardly be considered authentic because urate crystals or a positive murexid test was not demonstrated. We know of one instance of a tophus in the tongue<sup>40</sup> and tophi occurring in the heart muscle have been described.<sup>41, 42, 43, 44, 45</sup>

In this particular case urate crystals were demonstrated in the tophi of the ear, olecranon bursa and the finger. They were also observed in the cartilage, the synovial membrane, the periarticular fibrous tissue and in the subchondral bone spaces of the various joints biopsied.

The articular changes encountered in gout are dependent upon the amount of monosodium urate deposited, its location and the resulting reaction to such depositions.

From the observations in this case, it is apparent that articular deformity may result because of extensive fibrosis of the periarticular tissues subsequent to the urate deposition, thus producing contractures and limitation of motion.

If such deposition occurs in the synovial membrane or subsynovial tissues, the resulting proliferation may be sufficiently marked to produce extensive pannus which in turn may completely cover the articular cartilages and cause a true fibrous tissue ankylosis not unlike that seen in rheumatoid arthritis. Such joints can subsequently go on to true bony ankylosis.<sup>8, 9, 12, 14, 46</sup> The pannus may invade or completely destroy the articular cartilage and calcified zone of cartilage with subsequent invasion of the subchondral bone spaces with destruction of the bone trabeculae. These changes lead to the typical punched-out areas seen on the roentgenograms. The pannus in gout differs from that of rheumatoid arthritis in that one can always demonstrate islands or masses of urate crystals in the pannus, provided the tissues are placed in special fixatives. It would appear that if urate deposition occurs primarily in the subchondral spaces, the accompanying vascular infiltrated fibrous tissue proliferation may be sufficiently marked to destroy bone trabeculae and produce the same typical punched-out areas previously described.

Deposition of urates confined solely to the articular cartilage will result in marked cartilage changes such as thinning, pits, depressions, fissures, crevices, diminution in number, scattering and clumping of cartilage cells. From the observations in this case, it is apparent that urate deposition in the articular cartilage can be sufficiently injurious to explain the development of degenerative joint disease or hypertrophic arthritic changes<sup>33</sup> of a more advanced character than would ordinarily be encountered in an individual this age.<sup>33, 34, 35</sup> Such changes were very marked in the knees of this patient (figure 8). The degenerative joint changes are in direct relation to the extent of the urate deposition and not merely an expression of long-continued use and increasing age. Therefore, we must appreciate that the deposition of monosodium urate in the articular cartilage can be responsible for the early appearance of extensive degenerative joint disease changes.

From what has been observed in this case, it must be apparent that all the described pathological changes may occur in any one joint.

Changes such as were encountered in this case have been reported previously.<sup>6, 7, 8, 9, 10, 11, 12, 13, 14</sup> Virchow in 1868<sup>6</sup> described a case of gout in which complete fibrous ankylosis of the phalangeal joint of the great toe took place. He stated that urate deposits were to be found not only in the cartilages, the thick layers of the periosteum, and the ligaments, but also in the fibrous tissue obliterating the joint space, within the joint itself. Isolated foci of uratic deposit were also seen in the marrow spaces of spongy bone. In 1876, Litten<sup>15</sup> described a very severe case of gout in a patient of 41, in whom the first attack had presumably occurred at the age of eight.



The hips, knees, shoulders, right elbow, wrists, fingers, and toes were all completely or partially ankylosed. In the large joints, the synovial membrane, the fibrous capsule, the ligaments, and the cartilages were all found to be covered with a thick layer of white, shiny urates having the consistency of ointment. The semilunar cartilages of the knees were almost completely destroyed. In the cartilages, the urate deposits were found exclusively in the intercellular substance, in decreasing amounts toward the epiphyseal border. The ankyloses were regarded as fibrous ankyloses with deformity and shrinking of the synovial capsule. A number of foci of urate deposits were found in the spongy bone of the epiphyses, as well as in the epiphyseal periosteum and perichondrium. In addition, urate deposits were present in the kidneys to a marked degree. The larynx was involved in the same manner. Amyloid deposit was noted in the arteries of the spleen, and amyloidosis of the kidneys was present. Although all of these changes have more recently been described in great detail in single joints by Pommer<sup>2</sup> and Brogsitter,<sup>14</sup> it is important to appreciate that generalized ankylosis due to gout is rare.

Certain authors have reported that rheumatoid arthritis and gouty arthritis are occasionally encountered in the same individual.<sup>38, 39</sup> The proof presented is anything but convincing. In all such instances, biopsies should be obtained if possible. This is the only means by which one can prove or disprove such a statement. In this case there were many aspects (particularly the physical and roentgen-ray findings) which closely resembled rheumatoid arthritis. In addition, positive streptococcal agglutination tests were obtained on a number of occasions. Some workers might consider such evidence sufficient to make a diagnosis of rheumatoid arthritis, yet biopsy of four joints demonstrated very clearly that the joint changes present were due solely to the deposition of urates in the periarticular tissue, synovial membrane, subsynovial tissue, cartilage and subchondral bone spaces. Without the biopsies, it would have been extremely difficult for us to prove that the joint deformities and ankyloses were due to gout.

This case serves to emphasize the fact that widespread ankylosis due to gout is occasionally encountered. It also illustrates another point, namely, that if one becomes gout-conscious, the incidence of gout seemingly increases. This increase, however, is directly related to one's knowledge of the disease. As it increases, so does the incidence of gout. If one is to demand the presence of tophi, characteristic roentgen-ray changes and hyperuricemia before making the diagnosis of gout, many cases of "presumptive" gout will go on for years undiagnosed or mislabelled. Our interest in this disease was aroused some years ago by the insistence of Hench that cases of "presumptive" gout are frequently not recognized. That such an assumption was correct has been borne out. Increasing suspicion of its existence has resulted in a marked increase in the number of cases so diagnosed in this clinic each year. This experience is similar to that of Hench.<sup>48</sup>

## SUMMARY

1. The findings in a severe case of gout with rapidly appearing widespread ankylosis are presented.

2. Many of the clinical features resembled those seen in an individual with advanced rheumatoid arthritis.

3. The diagnosis of gout in this case was confirmed by demonstrating monosodium urate crystals in the tophi of the ear, the finger and the olecranon bursa. They were also demonstrated in the periarticular structures, synovial membrane, subsynovial tissue, subchondral bone spaces and articular cartilage of the four joints examined.

4. The histological changes seen in the astragalotibial joint simulate those seen in advanced rheumatoid arthritis except that the pannus responsible for the complete fibrous ankylosis contained innumerable urate deposits. Such urate deposits induce marked proliferation of the synovial and subsynovial tissue (pannus). Once this has formed, the ensuing changes take place rapidly.

5. Urate deposits in the articular cartilage resulted in sufficient articular cartilage damage to allow marked degenerative joint changes (hypertrophic arthritis) to appear at a much earlier age than they are ordinarily encountered.

6. The differential diagnosis of acute, recurrent gouty arthritis is discussed.

7. The clinical features of "presumptive" gout are presented in detail with the hope that more physicians will be made gout-conscious.

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THE URIC ACID IN THE SERUM OF GOUTY AND  
OF NON-GOUTY INDIVIDUALS: ITS DETER-  
MINATION BY FOLIN'S RECENT  
METHOD AND ITS SIGNIFI-  
CANCE IN THE DIAG-  
NOSIS OF GOUT \*

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SINCE the original description by Folin and Denis <sup>1</sup> in 1913 of a colorimetric method for the estimation of uric acid in blood, and the application of this method in the same year by Pratt <sup>2</sup> to the study of gout, scores of publications have concerned themselves with both methods and with blood uric acid values in health and disease. To review this vast literature completely would serve no purpose, especially as many divergent results have had as their basis methods of estimation fraught with various sources of error. The present communication describes the use of the most recent Folin method in the study of a number of gouty and of non-gouty individuals. In substance the results of this study constitute an amplification and confirmation of the earlier findings of Pratt.<sup>2</sup>

THE DETERMINATION OF URIC ACID IN SERUM

Since the spring of 1933 the latest Folin <sup>3</sup> method for the determination of blood uric acid has been in use in this laboratory. In the course of the application of this method to the study of gouty patients the procedure has been adhered to with but one minor modification to be described below.

In his last paper Folin <sup>3</sup> recommended the use of improved reagents on unlaked whole blood filtrates. He had previously <sup>4</sup> proposed the use of unlaked blood filtrates in order to avoid the presence of substances which inhibit the color reaction, and of reactive, non-uric acid substances, both of which are apparently set free from laked blood cells. The unlaked blood filtrates were thought to contain the readily diffusible products of the blood cells, but were supposedly free of disintegration products of the cells. With the improvement in the sensitivity and specificity of the reagents Folin believed that the problem of the accurate determination of uric acid in small quantities of blood had been satisfactorily solved.

Early in the course of this work, on the suggestion of the late Professor

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A considerable part of this work was carried out during a collaborative study of gout by Dr. John H. Talbott of this clinic, and the author.



Folin, we estimated the uric acid in both whole blood and in plasma of the same sample. During frequent determinations of the blood uric acid in one case of gout, it soon became apparent that the whole blood values, measured in strict accordance with Folin's directions, exhibited a degree of fluctuation far greater than the variation in simultaneously determined plasma uric acid values. The method of handling the blood has been

TABLE I  
Uric Acid Extracted from Red Blood Cells

Blood, Number of Sample	I Uric Acid, Plasma, Observed, mg. per cent	II Uric Acid, Unlaked Whole Blood, mg. per cent	III Cell Volume, per cent	IV Plasma Volume, per cent	V Uric Acid, Plasma, Calculated, mg. per cent	VI Uric Acid, Extracted (V-I), mg. per cent
1.....	8.27	4.61	48.30	51.70	8.90	0.63
2.....	8.73	5.53	42.65	57.35	9.64	0.91
3.....	9.44	6.38	43.40	56.60	11.3	1.86
4.....	9.68	5.80	45.00	55.00	10.6	0.92
5.....	9.78	5.84	44.65	55.35	10.6	0.82
6.....	9.86	6.20	43.55	56.45	11.0	1.14
7.....	9.90	6.64	48.80	51.20	13.0	3.10
8.....	10.0	6.90	45.95	55.05	12.5	2.50
9.....	10.5	6.37	45.50	55.50	11.5	1.50
10.....	10.5	6.83	41.24	58.76	11.6	1.10
11.....	10.6	7.05	40.10	59.90	11.8	1.20
12.....	10.8	6.50	47.00	53.00	12.3	1.50
13.....	10.9	6.20	48.90	51.10	12.1	1.20
14.....	11.1	7.28	42.20	57.80	12.6	1.50
15.....	11.2	7.48	43.95	56.05	13.4	2.20
16.....	11.2	6.76	45.40	54.60	12.4	1.20
17.....	11.4	6.66	47.80	52.20	12.8	1.40
18.....	12.3	7.00	46.40	53.60	13.1	0.80
19.....	12.4	7.84	47.40	52.60	14.9	2.50
20.....	12.4	7.80	45.00	55.00	14.2	1.80
21.....	12.5	8.48	41.62	58.38	14.5	2.00
22.....	12.8	9.67	44.80	55.20	17.5	4.70
23.....	13.1	7.35	48.25	51.75	14.2	1.10
24.....	13.3	7.42	42.70	57.30	13.0	-0.30
25.....	13.3	7.93	47.00	53.00	15.0	2.70
26.....	13.4	8.96	42.30	57.70	15.5	2.10
27.....	13.5	9.32	47.82	52.18	17.9	4.40
28.....	13.9	10.1	51.00	49.00	20.6	6.70
					Average	1.97

previously described.<sup>5</sup> In brief, the venous blood, drawn without stasis from the subject under basal conditions, was treated with heparin and was then equilibrated with carbon dioxide at a tension of approximately 40 mm. of mercury.\* The equilibrated whole blood was then centrifuged under oil, and the plasma separated. Samples of both equilibrated whole blood and plasma were taken for analysis. Such analyses of 28 different blood samples, all from a patient suffering from gout, are given in table 1.

\* The author is indebted to Dr. John H. Talbott for carrying out the equilibrations.

These data demonstrate that with increasing plasma uric acid values the concentrations of whole blood uric acid do not increase regularly. We might assume, as Folin apparently did, that the uric acid determined in unclotted whole blood represents the uric acid in the plasma together with uric acid that has diffused from the red blood cells. If this assumption be true it would be expected that the determined values of plasma and whole blood uric acid would run parallel, inasmuch as uric acid appears to be freely diffusible between plasma and cells.<sup>6</sup> The data of columns I and II of table 1 do not show the expected parallelism. Knowing the plasma volumes it is possible to calculate, from the value of the whole blood uric acid, the concentration of uric acid in the plasma.\* Such calculations are presented in column V of table 1. It is evident that in every case but one (sample 24) the calculated *exceeds* the observed value of plasma uric acid concentration. The deviations of the calculated from the observed values are listed in column VI of table 1. It is seen that the deviations bear only a rough relation to the magnitude of the observed plasma uric acid values, the smallest being 0.63 mg. per cent, and the largest 6.7 mg. per cent. These deviations, which are obviously due to the extraction from the red blood cells of uric acid or of reactive, non-uric acid substances, are *variable* in magnitude, and determine the extreme variation of whole blood uric acid values among the samples with approximately equal plasma uric acid concentrations.

There appeared to be at least two possible explanations of the variable additional quantities of uric acid found in the whole blood samples. In the first place, although a sample of equilibrated whole blood was used for the determination, the handling of the specimen, fresh from the tonometer, involved rapid stirring in the atmosphere, pipetting of 1 c.c. from the sample into a 25 c.c. Erlenmeyer flask, and agitation after the addition of the sodium tungstate solution. It is obvious that this repeated exposure to the atmosphere of the sample resulted in a loss of carbon dioxide from the blood, and rendered it essentially non-equilibrated whole blood. The following experiment demonstrated the effect of the loss of carbon dioxide upon the apparent uric acid value. A sample of whole blood from a gouty individual was divided into two parts, one part stirred with heparin in an open vessel, the other part similarly treated under a layer of mineral oil. One c.c. of the latter portion was transferred under oil to the Erlenmeyer flask, and the protein was precipitated under oil. The whole blood uric acid in the portion exposed to the air measured 7.6 mg. per cent, while the portion handled anaerobically yielded a value of 6.8 mg. per cent. Differences in the same direction are shown by the data of table 2. In these experiments each sample of whole blood was divided into two parts, one part allowed to clot in a centrifuge tube under a layer of mineral oil, the other part in a centrifuge tube without oil, with both tubes kept at 4° C.

\* Calculated plasma uric acid = whole blood uric acid X 100/plasma volume.

TABLE II  
Uric Acid in Serum

Blood, Number of Sample	Serum of Blood Clotted under Oil, Uric Acid, mg. per cent	Serum of Blood Clotted in Air, Uric Acid, mg. per cent
1.....	10.5	11.0
2.....	10.3	10.8
3.....	10.0	10.6
4.....	9.7	10.1
5.....	7.7	7.7

for approximately  $1\frac{1}{2}$  hours. It was thus evident that exposure of the blood to the atmosphere, in four of five experiments, increased the apparent uric acid content, *not only of the whole blood, but also of the serum*. On the other hand, when precautions were taken to minimize the exposure of the blood samples to the air there were obtained serum uric acid values practically identical with those of plasma of the same *equilibrated* samples. In table 3 are presented data which indicated that allowing the blood to clot

TABLE III  
Comparative Uric Acid Concentration in Plasma and Serum

Blood, Number of Sample	Plasma of Equi- librated Blood, Uric Acid, mg. per cent	Serum of Blood- Clotted under Oil, Uric Acid, mg. per cent
1.....	12.6	12.0
2.....	11.6	11.6
3.....	11.2	11.4
4.....	10.5	10.5
5.....	10.1	10.2
6.....	6.7	6.6

under a layer of oil furnished serum uric acid values which closely approximated those of plasma that had been separated from the red blood cells under a physiological tension of carbon dioxide. On the basis of the fore-going data, therefore, wherever serum rather than plasma from equilibrated blood has been used, the serum has been derived from a sample of whole blood that has been allowed to clot under a layer of mineral oil. The blood was drawn into an oiled syringe; immediately thereafter the tip of the needle was inserted under the surface of a few cubic centimeters of mineral oil contained in a centrifuge tube, and the blood was then expelled under the oil. All of the uric acid values described below are based upon analyses of such sera, or of plasma of equilibrated blood.

That this apparent increase in uric acid content accompanying the slight loss of carbon dioxide depends upon a migration of uric acid or of reactive, non-uric acid substances, from the blood cells into the serum as the blood becomes more alkaline is suggested by the experimental data of Jacoby and

Friedel.<sup>7</sup> These authors studied the loss of uric acid from the plasma after the addition of known amounts of uric acid to whole blood maintained by phosphate buffers at pH 7.38, 7.17, and 6.46, respectively. In every one of 13 such experiments an increase in the pH was accompanied by greater recovery in the plasma of the added uric acid. A shift in the same direction of both native and of added uric acid has more recently been reported from this clinic by Talbott and Sherman.<sup>8</sup>

A second explanation of the variable increments of whole blood uric acid, over the calculated values of plasma content, was the possibility that the reagents used in precipitating the unlaked blood cells might extract from the cells uric acid, or reactive non-uric acid substances. This possibility has been rendered probable by the work of Heller.<sup>8</sup> He showed that *variable* amounts of uric acid (or of chromogenic material) could be washed out of the blood cells by the hypertonic sodium tungstate solution, and that additional but *inconstant* amounts were extracted during acidification with the sulfuric acid. The averages of a number of determinations were 1.32 mg. per cent extracted by the sodium tungstate alone, and 1.85 mg. per cent after the addition of the sulfuric acid. This latter value is of the same order of magnitude as the average of the present experiments (column VI, table 1).

Because of these variable degrees of extraction from the blood cells, it seemed desirable to give up whole blood uric acid determinations entirely, and to determine uric acid only in serum in the manner described above. Plasma or serum uric acid determinations have been employed in the past by many investigators, including Folin, Berglund, and Derick,<sup>9</sup> Thannhauser,<sup>10</sup> and Wiener and Wiener.<sup>11</sup>

#### THE RECOVERY OF ADDED URIC ACID

Two procedures have been commonly employed in the past to define the specificity and the accuracy of various methods for the determination of uric acid in blood, namely, a comparison between the results of colorimetry directly upon the blood filtrate with the values obtained after preliminary precipitation of the uric acid; and the extent of recovery of uric acid added to blood. That all of the color developed by the Folin 1933 reagents is probably due to uric acid is suggested by the fact that both the direct and the indirect methods yield practically identical values. In his last paper<sup>3</sup> Folin demonstrated that applying the reagents directly to the unlaked whole blood filtrates resulted in values no higher than those obtained after preliminary precipitation with silver nitrate. For this reason all of the values reported below represent *direct* determinations on the serum filtrate.

Throughout the literature concerning the determination of uric acid there have repeatedly cropped up reports of incomplete recoveries of uric acid added to whole blood.<sup>12</sup> The earlier claim of quantitative recoveries made by Folin and Wu<sup>13</sup> was within three years corrected by Folin,<sup>14</sup> who then admitted that losses of as much as 10 per cent of added uric acid might

be encountered. It was principally because of this incomplete recovery that Folin in 1930<sup>4</sup> turned to the use of *unlaked* whole blood filtrates, and demonstrated that the loss of added uric acid was not dependent solely upon adsorption of uric acid by the precipitated protein, but rather was due to the fact that something in laked blood filtrates *depressed* the color reaction. This inhibitory effect was apparently completely avoided when unlaked blood filtrates were used, as evidenced by the quantitative recoveries of uric acid added to such bloods.<sup>4</sup> Similarly, data presented by Folin in his last paper<sup>3</sup> showed that of uric acid added to whole blood from 94 to 100 per cent was recovered. On the other hand, data are not lacking which indicate substantial losses of uric acid added not to whole blood but to *plasma*. Thus Wiener and Wiener,<sup>11</sup> using the Folin 1922 reagents, found the following recoveries of small amounts of uric acid added to plasma: 72, 83, 95, 77, and 100 per cent respectively. Similarly, in the hands of the author the application of the Folin 1933 method to plasma or to serum has not consistently yielded quantitative recoveries of added uric acid. In table 4 are

TABLE IV  
Recoveries of Uric Acid Added to Plasma or Serum

Experiment Number	Uric Acid Added, mg. per cent	Uric Acid Recovered, per cent of uric acid added
1	3.33	96
2	4.00	61
3		91
4	5.00	80
5		86
6		86
7		86
8		87
9		88
10		92
11		94
12	10.00	87
13		87
14		88
15		88
16		89
17		90
18		91
19		92
20		93
21		93
22		93
23		93
24		95
25		96
26		96
27		97
28		99
29		99
30		102
Average		90



presented the results of 29 experiments. With the exception of one experiment the recoveries were 80 per cent or better, and in 16 experiments the recoveries exceeded 90 per cent. The recoveries could not be consistently bettered by the addition of the uric acid dissolved in the sodium tungstate solution, or by the delivery of the sulfuric acid at an extremely slow rate, with constant stirring of the precipitation mixture. On the other hand, that much of the loss is due to the adsorption of added uric acid by the *precipitated* protein is shown by the following recoveries, after the addition of 10 mg. per cent of uric acid *subsequent* to the precipitation of the protein: 96, 89, 99, 98, and 93 per cent, respectively. It must be concluded, therefore, that the present method for the determination of uric acid in serum may involve negative errors of an average magnitude of 10 per cent.

#### THE SERUM URIC ACID IN NON-GOUTY INDIVIDUALS

The serum uric acid was determined, under basal conditions, in 100 non-gouty adults. All of the subjects had been consuming a mixed diet. In most instances one such value was obtained for each individual; where more than one determination was performed the highest value has been recorded. Among 37 females the mean age was 39.2 years, and among 63 males the mean age was 44.5 years. Of the 100 subjects only 24 were considered free of organic disease. The remaining 76 subjects were hospital and private patients suffering from a variety of, for the most part, chronic diseases. In the choice of these non-gouty patients for the present study there were excluded only those suffering from renal disease with nitrogen retention, disease of the liver, and leukemia, conditions in which it is well established that abnormally high uric acid concentrations may be encountered.

In table 5 are presented the frequency distribution of the non-gouty

TABLE V  
Frequency Distribution of Serum Uric Acid Values in 100 Non-Gouty Individuals

Serum Uric Acid, mg. per cent	1.0-1.9	2.0-2.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9
63 Males.....	0	8	13	23	16	3
37 Females.....	1	6	7	16	7	0
100 Total.....	1	14	20	39	23	3

values of serum uric acid concentration. It is seen that the distribution of values among the males and the females is very similar, in each case at a maximum between 4.0 and 4.9 mg. per cent. The mean serum uric acid content among the males was  $4.4 \pm 0.09$ , among the females  $4.0 \pm 0.11$ , and among the entire 100 non-gouty individuals  $4.2 \pm 0.07$  mg. per cent, respectively.

Included in the data of table 5 are values from two patients who had passed uric acid vesical calculi, but without evidence of gout. The serum uric acid content in one case was 4.5 mg. per cent, and in the other case was 3.6 mg. per cent.

*The Serum Uric Acid in Non-Gouty Arthritis.* Twenty cases of non-gouty joint disease are included in the cases described above. The diagnosis in most of the 20 cases was arrived at only after exhaustive study. The serum uric acid values found in these cases are presented in table 6. It

TABLE VI  
The Serum Uric Acid in Non-Gouty Arthritis

Diagnosis	Case Number	Serum Uric Acid, mg. per cent
Rheumatoid Arthritis . . . . .	1	2.4
" " . . . . .	2	2.6
" " . . . . .	3	2.9
" " . . . . .	4	3.2
" " . . . . .	5	3.3
" " . . . . .	6	3.3
" " . . . . .	7	3.5
" " . . . . .	8	3.7
" " . . . . .	9	4.3
" " . . . . .	10	5.0
" " . . . . .	11	5.6
" " . . . . .	12	5.7
" " . . . . .	13	5.9
" " . . . . .	14 ✓	6.7
Hypertrophic Arthritis . . . . .	15	4.2
" " . . . . .	16	4.7
" " . . . . .	17	4.9
Gonorrheal Arthritis . . . . .	18	5.2
Multiple Foci of Osteomyelitis . . . . .	19 ✓	6.2
Arthritis or Periostitis, cause unknown . . . . .	20 ✓	6.7

is to be noted that the only cases among all of the non-gouty individuals in whom serum uric acid values in excess of 6.0 mg. per cent were found include three listed in table 6 (cases 14, 19, and 20). All were males; none showed any clinical evidence of gout; and in none was there evidence of impaired renal function or of hepatic disease. Case 14 suffered from spondylitis deformans (rheumatoid arthritis); case 19 was one of multiple foci of osteomyelitis; and case 20 was diagnosed arthritis or periostitis, cause unknown.

Similar *infrequent* instances of elevated blood uric acid values in chronic, non-gouty arthritis have been reported by Pratt.<sup>15</sup>

The mean serum uric acid among the 20 cases of non-gouty arthritis was  $4.6 \pm 0.20$  mg. per cent. This value exceeds the mean of the entire 100 non-gouty individuals by only  $0.4 \pm 0.21$  mg. per cent, a difference of no statistical significance.

#### THE SERUM URIC ACID IN GOUT

*Material.* The material of the present study consisted of 21 cases of gout. In nine cases the characteristic sodium urate crystals yielding a positive murexide test were obtained from tophi. In the remaining 12 cases



Case Number.....	1 F.M.	2 F.N.	3 K.H.	4 W.B.	
Age.....	21	28	44	73	
Diagnoses.....	Gout	Gout	Presumptive gout Chronic nephritis Cholelithiasis Nodular goiter with hy- pothyroidism Secondary anemia Cystitis	Gout Obesity Emphysema	Psoriasis
Tophi on ears.....	Present	Present	Absent	Present	
Tophi elsewhere.....			On tendons of dorsum of hands		
Morphological and chemical tests for sodium urate from tophi.....	+	+	Not examined	+	
Duration of gout.....	9 years	7 years	6 years	25 years	
Chronicity of gout.....	Numerous joint deformities with roentgen- ray changes	Numerous joint deformities with roentgen-ray changes	Numerous joint de- formities with roentgen- ray changes	Numerous joint deformities with roentgen- ray changes	
Frequency of attacks of acute gout.....	Every 1 to 3 months last few years	Every 4 to 6 months, with increasing de- formities of many joints; every few weeks, last few years	Every 1 to 2 months last few years; 5 attacks in last three months	Every 6 months first 22 years, every few months last 3 years, with chronic joint pain often be- tween attacks	Every 2 to 3 months last few years
Blood pressure.....	120/80	124/90	104/76	138/62	
Maximum urinary specific gravity Single specimen.....	1.030			1.022	
Urine concentration test.....		1.012	1.013		
Excretion of phenolsulphonephthalein 15 minutes after intravenous injection of 6 mg.....	45-48%	13%	0-8% in 5 tests	15%	
Blood non-protein nitrogen, mg. per cent Whole blood.....				29	
Serum.....	17-26	20-27	34-38		
Date of uric acid determinations.....	7/3/33-6/28/34	2/6-3/30/35	4/6/34-9/18/35	2/13-3/19/35	11/1/35
Total number of uric acid determinations.....	73	36	19	14	
Serum uric acid, mg. per cent	Diet	Acute Gout	Medication		
	Mixed	0	0	Number of determinations Single value Range Mean	1 12.9
			+	Number of determinations Single value Range Mean	2 13.3-13.9 13.6
		+	0	Number of determinations Single value Range Mean	3 12.3-14.8 13.2
			+	Number of determinations Single value Range Mean	1 11.4
	Purine-free	0	0	Number of determinations Single value Range Mean	25 9.1-13.7 11.0±0.18
			+	Number of determinations Single value Range Mean	4 9.7-12.7 11.3
		+	0	Number of determinations Single value Range Mean	29 8.3-13.5 10.7±0.17
			+	Number of determinations Single value Range Mean	8 8.1-13.4 10.4±0.38



TABLE VII  
Serum Uric Acid in Gout

[illegible]



TABLE VII  
Serum Uric Acid in Gout

2 F.N.	3 K.H.	4 W.B.	5 J.B.	6 E.F.	7 I.F.	8 C.G.	9 F.S.	10 O.Me.	11 L.S.	
28	44	73	46	53	46	46	65	53	40	
Gout	Presumptive gout Chronic nephritis Cholelithiasis Nodular goiter with hy- pothyroidism Secondary anemia Cystitis	Gout Obesity Emphysema	Presumptive gout Obesity	Gout	Presumptive gout Obesity	Presumptive gout	Presumptive gout	Gout Psoriasis	Presumptive gout	
Present	Absent	Present	Absent	Present	Absent	Absent	Absent	Present	Absent	
	On tendons of dorsum of hands							Olecranon bursa		
+	Not examined	+		+				+		
7 years	6 years	25 years	12 years	11 years	10 years	5 years	30 years	22 years	13 years	
Numerous joint de- formities with roentgen-ray changes	Numerous joint de- formities with roentgen- ray changes	Numerous joint deformities with roentgen- ray changes	None	None	None	None sympto- matically, but roentgen-ray changes in both feet	Mass in olecranon bursa	None sympto- matically, but roentgen-ray changes in both feet	Never free of joint symptoms, numerous joint deformities	
Every 4 to 6 months, with increasing de- formities of many joints; every few weeks, last few years	Every 1 to 2 months last few years; 5 attacks in last three months	Every 6 months first 22 years, every few months last 3 years, with chronic joint pain often be- tween attacks	Every few weeks	Every 3 to 6 months	Every 9 months; 3 attacks last 3 months	Every 4 to 6 months; 6 attacks last 6 months	Every 1 to 1½ years	4 attacks last 6 months	Every few weeks to few months	
124/90	104/76	138/62	120/80	120/70-150/100	134/90-120/82	140/90	150/80	144/88	—	
		1.022		1.024	1.020		1.016	1.017	—	
1.012	1.013		1.020			1.037				
13%	0-8% in 5 tests	15%	40%	—	—	34%	—	—	—	
		29		28			30	38		
20-27	34-38		19		21	23			35	
2/6-3/30/35	4/6/34-9/18/35	2/13-3/19/35	11/17/36-6/22/37	9/17/35-6/24/37	3/4-7/3/37	4/12-6/21/37	10/1-10/2/35	3/2/35	3/16/35	
36	19	14	8	5	4	4	2	1	1	
			6 6.6-10.0 8.1±0.39	2 7.6-7.7 7.7						
	5 9.3-14.2 10.9		2 7.5-9.6 8.6	3 7.5-8.7 8.1	3 7.2-9.6 8.1	2 8.7-11.1 9.9				
	1 10.1						1 8.2	1 7.3		
							1 5.7			
20 10.5-14.5 12.4±0.20	4 8.2-8.8 8.6	9 6.0-7.4 6.9±0.08				2 7.3-8.3 7.8				
3 8.9-10.4 9.7	1 9.5	4 5.2-7.0 6.5								
13 7.4-13.6 12.1±0.31	6 8.3-9.1 8.8±0.06	1 7.0							1 9.4	
	1 8.8				1 7.7					

[illegible]



demonstrable or accessible tophi were not present. In these cases the diagnosis was based upon a characteristic history and physical finding, and was agreed upon by several observers. Both clinical and metabolic descriptions of cases 1 and 3 have been previously published<sup>5</sup>; case 2 forms the subject of a contemporary study.<sup>16</sup> Data on case 11 were reported in 1926 by Folin, Berglund, and Derick.<sup>9</sup>

In table 7 are presented all relevant data concerning the gouty subjects. All were males, with the exception of case 3. The ages of the patients ranged between 21 and 73 years. The duration of the disease varied from 4 months to 36 years. In ten cases chronicity of the disease was evidenced by deformities of joints or by characteristic roentgenologic bony lesions. In only seven patients was chronic gouty arthritis present (cases 1, 2, 3, 4, 11, 17, and 18). In the remaining 14 cases recurrent attacks of acute gouty arthritis had left no joint defects. All types of severity of gout were represented by these cases, ranging from case 2, of chronic gouty arthritis with multiple extensive ankyloses, and with superimposed attacks of acute gouty arthritis at intervals of a few weeks, to case 14, free of chronic changes and free of gouty attacks since the initial one three years previously.

In six cases there was present some degree of renal insufficiency, which by itself partially invalidates the diagnostic significance of the elevated uric acid values. The evidence for renal insufficiency was furnished principally by the non-protein nitrogen content of the blood and by the excretion of intravenously injected phenolsulphonephthalein, and in some cases by the urinary specific gravity during a concentration test. The values of non-protein nitrogen content in table 7 are to be interpreted in terms of the normal range of 20 to 35 mg. per cent in whole blood, and of 20 to 30 mg. per cent in serum. The excretion of phenolsulphonephthalein 15 minutes after the intravenous injection of 6 milligrams of the dye amounts to at least 25 per cent in normal individuals.<sup>17</sup> On the basis of these tests case 3 was considered one of moderate renal insufficiency, while cases 2, 11, 16, 17, and 18 represented minimal degrees of renal impairment.

Disease of the liver occurred in only one instance, case 17, in which acute yellow atrophy was present, accompanied by marked disturbance of hepatic function.

Among the 21 cases of gout the serum uric acid was determined on a total of 177 occasions, under various conditions to be described in detail below. On 174 occasions (98 per cent of total) the serum uric acid content exceeded 6.0 mg. per cent; on 167 occasions (94 per cent of total) the value exceeded 7.0 mg. per cent. Four values ranged between 14.1 and 14.8 mg. per cent.

*The Influence of a Purine-Free Diet Upon the Serum Uric Acid Level.* That the consumption of a purine-free diet over a prolonged period is often followed by a slight depression of the blood uric acid level in gouty individuals has been reported by many investigators. The present data are

necessarily limited by the fact that the few subjects who consumed a purine-free diet did so for *relatively short periods*. Thus the longest such period, during which the serum uric acid was determined frequently, was three months (case 1). Moreover, there are lacking for comparison sufficient data on the same subject obtained while on a mixed diet. All of the data are depicted in table 7 in relation to other possible influences on the serum uric acid level. In no single case were there gathered sufficient values to permit a statistical comparison of the effect of variation only in the diet, with all other influences equal. The few individual values of serum uric acid content while a purine-free diet was consumed *appear* to be slightly lower than those obtained while the subjects consumed a mixed diet (cases 1 and 3). On the other hand, it is evident that a purine-free diet, consumed over short periods, did not result in a fall of the serum uric acid content to a non-gouty level. Thus, of a total of 61 determinations among five patients (cases 2, 3, 4, and 8), free of acute gout and maintained on a purine-free diet without specific medication, only one value was as low as 6.0 mg. per cent, while 55 values exceeded 7.0 mg. per cent. Under similar restrictions of diet and of medication 51 values were obtained among six patients during attacks of acute gout. None of these values fell below 7.0 mg. per cent.

*The Influence of Various Drugs Upon the Serum Uric Acid Level.* In many instances the serum uric acid was determined while the patients were under the influence of one or more of several drugs which have been found, by many observers, to often lower the blood uric acid level. These drugs are aspirin, colchicin, and salyrgan. None of the subjects of the present study were under the influence of cinchophen or of related materials.

It may be seen in table 7 that only scanty data were obtained in any one patient while medication was administered, and *while a purine-free diet was consumed*, either during an interval between attacks of acute gout or during an attack. In case 1 on a purine-free diet and during several gouty attacks a total of 29 determinations of serum uric acid were performed while drugs were withheld; the mean of these values was  $10.7 \pm 0.17$  mg. per cent. While drugs were administered (aspirin, as much as 4 grams daily for several days, or colchicin, as much as 8 milligrams on any one day) 8 determinations of serum uric acid yielded a mean of  $10.4 \pm 0.38$  mg. per cent.

In a few instances drugs were apparently responsible for significant changes in the serum uric acid content. On one occasion the administration to case 1 of 3.0 milligrams of colchicin was followed by an apparent temporary fall of the uric acid to 8.5 mg. per cent (depicted in figure 1, February 6, 1934), which succeeded a marked urinary excretion, on February 5, of 1.42 grams of uric acid. It is, of course, possible that this temporary fall was a result of some influence other than the colchicin. One of the lowest serum uric acid values among the entire 177 values was found in case 9 (table 7). During the nine days prior to the first determination (October



1, 1935) the left olecranon bursa was involved in an acute attack of gouty arthritis; by October 1 the active pain was absent, but pain on motion and moderate swelling and tenderness of the elbow were still present. During the previous five days the patient had consumed 2.6 grams of aspirin daily. The serum uric acid on October 1 was 5.7 mg. per cent. Medication was withheld. The following day the serum uric acid was 8.2 mg. per cent. That this low value of 5.7 mg. per cent was related to the administration of the aspirin rather than to other influences is rendered likely by further data to be presented below.

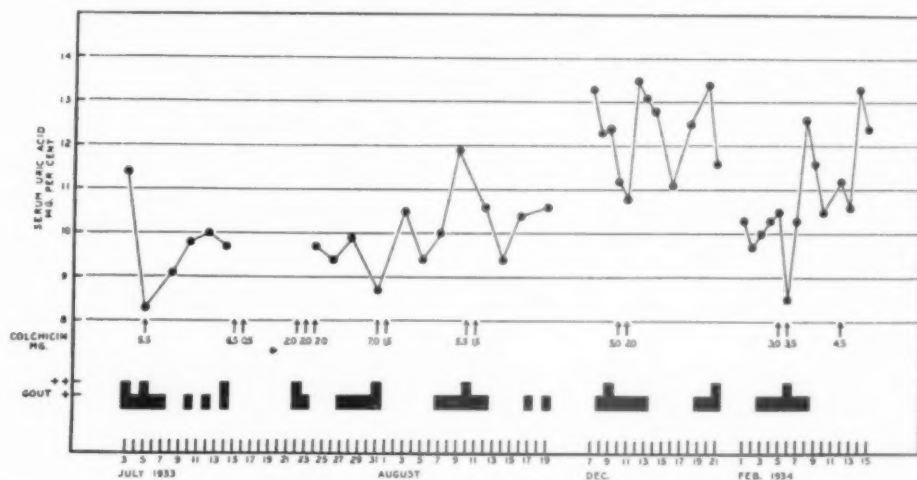


FIG. 1. Case 1. Serum uric acid levels in relation to acute attacks of gout and to administration of colchicine. (Purine-free diet, constant fluid intake of 2000 c.c. daily.)

In four experiments among three patients the intravenous administration of salyrgan was followed by a significant temporary fall of the serum uric acid. Two of these experiments are depicted in figure 2, and a third in figure 3. In the latter instance the serum uric acid fell to 5.2 mg. per cent, the lowest value among the entire 177 determinations. In a fourth experiment on case 1 a serum uric acid level of 11.9 mg. per cent was succeeded, on the day after the intravenous injection of 2 c.c. of salyrgan, by a value of 8.1 mg. per cent. In all of the above experiments the lowering of the serum uric acid levels followed a markedly increased urinary excretion of uric acid.

*The Relationship of the Serum Uric Acid Level to the Attack of Acute Gouty Arthritis.* The possible relationship of the blood uric acid level to the attack of acute gouty arthritis has been studied by many observers, with almost as many divergent results as a consequence. That the blood uric acid rises just before an attack is a view shared by Lichtwitz and Steinitz,<sup>18</sup> Lucke,<sup>19</sup> and by Chrometzka.<sup>20</sup> That no such pre-attack rise occurs was stated by Gudzent.<sup>21</sup> Pratt,<sup>15</sup> writing in 1921, thought that the blood during

an acute attack usually contains slightly more uric acid than at other times. Rathery and Violle<sup>22</sup> and Thannhauser<sup>10</sup> held that the uric acid falls during an attack. Finally, Richter<sup>23</sup> maintained that the blood uric acid at the beginning of an attack is *either* elevated or depressed.

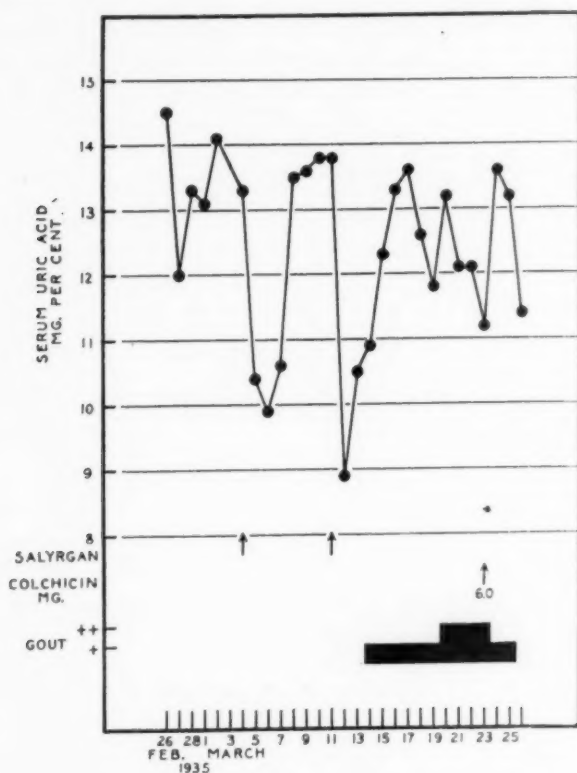


FIG. 2. Case 2. Serum uric acid levels in relation to administration of salyrgan and to acute attack of gout. (Purine-free diet, constant fluid intake of 2000 c.c. daily.) On each day denoted by an arrow 1 c.c. of salyrgan was injected intravenously, after blood was drawn for analysis.

In the opinion of the present writer, none of the above generalizations are based upon sufficient experimental evidence. It is apparent that critical evidence must include very frequent observations of blood uric acid throughout an interval between acute attacks and during the attack of acute gouty arthritis, under controlled conditions of diet and of medication. The present data constitute only an approximation to this ideal. In figure 2 are depicted frequent observations of the serum uric acid in case 2 over a period of 29 days. It is evident that prior to the administration of salyrgan on March 4, during an asymptomatic interval, the serum uric acid *fluctuated* considerably, and that similar *fluctuation* took place during the twelve days of the attack of acute gout. (Any possible change of the uric acid level

just prior to the attack was, of course, masked by the effect of the salyrgan administered on March 11.) Quantitatively much less marked variations were found in case 3, depicted in figure 4. These observations have been

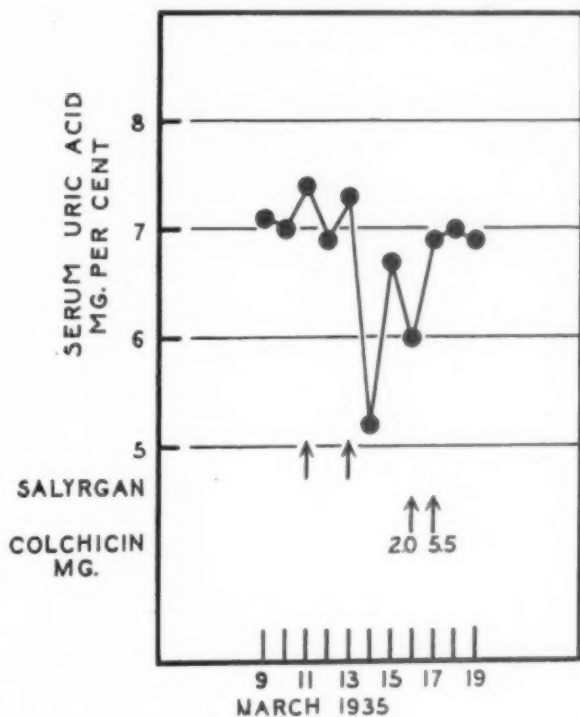


FIG. 3. Case 4. Serum uric acid levels in relation to administration of colchicin and salyrgan. (Purine-free diet, constant fluid intake of 2000 c.c. daily.) On each day denoted by an arrow 1 c.c. of salyrgan was injected intravenously after blood was drawn for analysis.

included in a previous report.<sup>5</sup> It is evident that the slight fall in the serum uric acid between April 6 and 10 might have been due to the change from a mixed diet to a purine-free diet on April 6, rather than related to the first attack of acute gout. During the following asymptomatic interval prior to the second attack of acute gouty arthritis the serum uric acid *apparently* declined, and then *apparently* rose during the first two days of the attack. More extended observations were made in case 1 and are presented in figure 1. (The data of December 7 to 21 have been included in a previous study.<sup>5</sup>) In this case it is evident that the serum uric acid values, other than those possibly related to the administration of colchicin, showed a high degree of fluctuation and bore no consistent relation to the acute attacks. Any apparent change just prior to or during the attacks was matched by equally apparent changes during the asymptomatic intervals.

It seems to the writer that the data described above illustrate the futility

of seeking evidence of a change among the highly variable successive serum uric acid values by mere *inspection* of the uric acid curves. It was on the basis of such observations that the several different generalizations in the

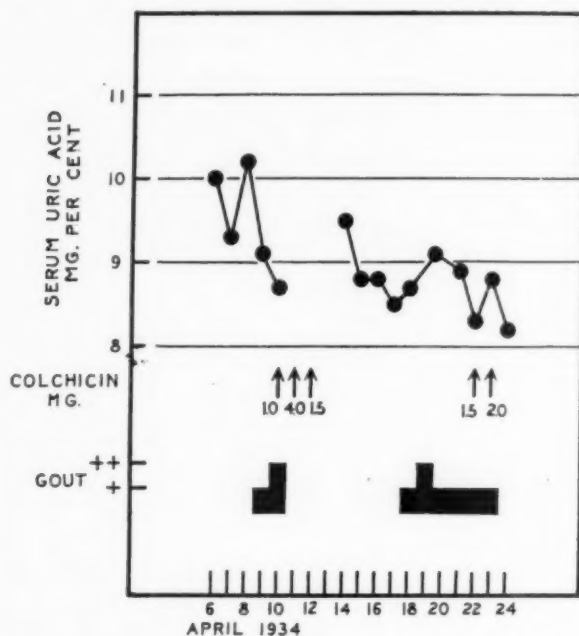


FIG. 4. Case 3. Serum uric acid levels in relation to acute attacks of gout. (Purine-free diet, constant fluid intake of 2000 c.c. daily.)

literature were founded. Rather, the inherent variability of serum uric acid values requires the statistical treatment of a large number of such values. In two gouty subjects sufficient data were collected to justify a statistical analysis. All of the data on case 2, obtained while the patient consumed a purine-free diet and while medication was withheld, are included in table 7. It is seen that the mean of a total of 20 serum uric acid values collected during all parts of asymptomatic intervals was  $12.4 \pm 0.20$  mg. per cent; while the mean of 13 values measured during all parts of acute attacks of gouty arthritis was  $12.1 \pm 0.31$  mg. per cent. Similar but more extended observations were made in case 1. In table 7 are presented all of the serum uric acid values obtained while the patient consumed a purine-free diet without medication, in relation to 18 attacks of acute gouty arthritis over a period of one year.

It is seen that the mean of 25 serum uric acid values during asymptomatic intervals was  $11.0 \pm 0.18$  mg. per cent, while a practically identical mean of  $10.7 \pm 0.17$  mg. per cent was found among 29 determinations during acute attacks. Thus, when all phases of asymptomatic intervals were compared with all phases of acute attacks of gout in these two cases, no change

of the serum uric acid was observed. On the other hand, a more detailed analysis of the data in case 1 yielded a different interpretation. In table 8 are presented the serum uric acid values in relation to finer sub-divisions of

TABLE VIII  
Serum Uric Acid Levels in Several Phases of Acute Attacks of Gouty Arthritis  
Case 1, Purine-free diet, no medication

	Intervals		Acute Attacks of Gouty Arthritis	
	Earlier than 3 Days Preceding Attacks	Within 3 Days Preceding Attacks	First 2 Days	Subsequent to First 2 Days
Number of determinations.....	12	13	12	17
Range, serum uric acid, mg. per cent..	10.5-13.3	9.1-13.7	9.7-13.4	8.3-13.5
Mean, serum uric acid, mg. per cent...	11.7 $\pm$ 0.18	10.3 $\pm$ 0.25	10.6 $\pm$ 0.22	10.8 $\pm$ 0.24

the intervals and of the periods of acute gouty arthritis. It is evident that *during the three days prior to the acute attacks the serum uric acid fell* from a previous mean of  $11.7 \pm 0.18$  mg. per cent to one of  $10.3 \pm 0.25$  mg. per cent, a significant difference of  $1.4 \pm 0.31$  mg. per cent. The additional data of table 8 demonstrate that *during the gouty attack the serum uric acid remained unchanged.*

*The Serum Uric Acid Level in Relation to the Severity of Gout.* In only four of the present 21 cases of gout were there obtained a sufficiently large number of serum uric acid values, under comparable conditions of diet and of medication, to justify an attempt to correlate the height of the uric acid level with the severity of the disease. On the basis of frequency and severity of attacks, and the extent of chronic joint deformities, it was considered by several observers that the four cases, in the order of their severity, were cases 2, 1, 3, and 4. In table 7 it is seen that during asymptomatic intervals (purine-free diet, no medication) the means of the serum uric acid values of these cases were  $12.4 \pm 0.20$ ,  $11.0 \pm 0.18$ , 8.6, and  $6.9 \pm 0.08$  mg. per cent, respectively. During attacks of acute gouty arthritis (purine-free diet, no medication) the means were  $12.1 \pm 0.31$ ,  $10.7 \pm 0.17$ , and  $8.8 \pm 0.06$  mg. per cent, respectively. (Data are lacking in case 4 in this category.) These respective differences in mean values are statistically significant. These data suggest, therefore, that in these four cases a more severe degree of gout was accompanied by a higher level of the serum uric acid.

Among the remaining 17 cases the serum uric acid values were insufficient in number to adequately characterize the uric acid level of any one case. However, the heights of the individual serum uric acid values did not appear related to such clinical aspects as the presence or absence of



chronic gouty arthritis or of tophi, the duration of the disease, or the frequency of attacks of acute gouty arthritis. With the exception of one of two values in case 9 (*vide supra*), the serum uric acid in every gouty individual was elevated.

*The Serum Uric Acid Level Among Close Relatives of Gouty Individuals.* As early as 1916 Folin and Denis<sup>24</sup> reported "a normal man of a gouty family" with an elevated whole blood uric acid (4.0 mg. per cent). As far as the present writer is aware, similar additional studies have not been published in the vast literature concerning gout and uric acid in the blood. Although a systematic investigation of the uric acid metabolism of close relatives of gouty individuals has not been carried out, the following observations require mention. The serum uric acid was determined in three individuals, all adult males, and completely free of a history or physical signs of joint disease. In all the non-protein nitrogen content of the blood was normal. The following serum uric acid values were found: a son of case 4, 6.7 mg. per cent,\* a son of case 6, 7.7 mg. per cent; and a brother of case 5, 8.4 mg. per cent, respectively.

*The Significance of the Serum Uric Acid Level in the Diagnosis of Gout.* It is evident from the foregoing presentation that in only a few instances among the 177 determinations of the serum uric acid in 21 cases of gout, under various conditions, were the values within the range established in the 100 non-gouty subjects. Thus in case 4 (see figure 3 and table 7), among 14 determinations performed over a period of one month, one value of 5.2 mg. per cent followed the administration of salyrgan on the previous day; three other values, unrelated to medication, were 6.0, 6.6, and 6.7 mg. per cent, respectively; while the remaining 10 values ranged between 6.9 and 7.4 mg. per cent. In case 9 the value of 5.7 mg. per cent was found at the end of a five-day period in which 2.6 grams of aspirin were consumed daily; a second determination yielded a value of 8.2 mg. per cent. Of the total 177 values, therefore, 175 values ranged between 6.0 and 14.8 mg. per cent. In contrast, 97 of 100 determinations among 100 non-gouty individuals yielded serum uric acid values less than 6.0 mg. per cent; three of the 100 values ranged between 6.0 and 6.7 mg. per cent.

The high serum uric acid values found in three relatives of gouty individuals have been described above. This finding must obviously be brought to bear upon the interpretation of an elevated uric acid level in the absence of gout, renal insufficiency, disease of the liver, or leukemia.

Comparable with the present serum uric acid values in gout are the plasma uric acid levels ranging between 6.5 and 10.7 mg. per cent, found in 11 determinations among nine gouty individuals by Folin, Berglund, and Derick.<sup>9</sup>

As far as the author is aware, the only other series of determinations, among gouty individuals, approaching the high proportion of elevated uric acid values of the present study is that of Jordan and Gaston.<sup>25</sup> These

\* This individual was studied in collaboration with Dr. John H. Talbott.

workers used the Folin 1930 method on unclaked whole blood. The upper limit of normal they took as 4.0 mg. per cent. In 53 determinations among 17 cases of gout the whole blood uric acid exceeded 4.0 mg. per cent in 47 instances.

The modern literature concerning the blood uric acid in gout, on the basis of older analytical methods, ranges between the view expressed by Thannhauser<sup>10</sup> that an elevated value is a constant finding in gout, to the observations by Gudzent<sup>26</sup> of *normal whole blood uric acid values in one-third* of 26 cases of gout. Similar to the latter findings were the observations reported in 1928 by Hench, Vanzant, and Nomland.<sup>27</sup> Among 100 cases of gout these authors found *normal whole blood uric acid levels in 28 cases*. Writing as late as 1936 Hench<sup>28</sup> found that *the whole blood uric acid was constantly elevated only in untreated chronic gouty arthritis*.

As far as the writer is aware, the present 177 determinations of the serum uric acid among 21 cases of gout, representing all types of the disease, under a variety of conditions, constitute the most extensive study of the problem of uricemia in gout. The results of this work amply confirm the original observations by Pratt<sup>2</sup> in 1913, based upon the use of the forerunner of modern colorimetric analytical methods, that hyperuricemia is practically constant in untreated gout. With the present method of estimation hyperuricemia is defined as a serum uric acid content in excess of 6.0 mg. per cent.

#### SUMMARY

The determination of uric acid in blood by means of the Folin 1933 method yielded experimental evidence for the view that analysis of *serum*, derived from blood allowed to clot under oil, furnishes more valid data than does *whole blood*.

The fasting uric acid in 100 non-gouty individuals consuming a mixed diet ranged from 1.9 to 6.7 mg. per cent, with a mean of  $4.2 \pm 0.07$  mg. per cent. In 97 individuals the serum uric acid was less than 6.0 mg. per cent.

The serum uric acid was determined on 177 occasions in 21 cases of gout, under various conditions. The serum uric acid values ranged from 5.2 to 14.8 mg. per cent. On 174 occasions (98 per cent of total) the value exceeded 6.0 mg. per cent; on 167 occasions (94 per cent of total) the value exceeded 7.0 mg. per cent.

The consumption by gouty individuals of a purine-free diet during periods shorter than three months did not significantly influence the serum uric acid level. The administration of aspirin, colchicin, and salyrgan to gouty individuals on several occasions was followed by an apparent temporary fall of the serum uric acid level.

The serum uric acid, frequently determined in four gouty individuals, apparently exhibited marked fluctuation both during asymptomatic intervals and during attacks of acute gouty arthritis. An intensive study of one case

of gout over a period of one year demonstrated a significant fall of the mean serum uric acid level during a three-day period preceding attacks of acute gouty arthritis; during the attacks the serum uric acid level remained unchanged.

Among four cases of gout an apparent direct correlation was found between the height of the serum uric acid level and the severity of the disease.

The serum uric acid was determined in the son of each of two gouty individuals, and in the brother of a third gouty individual. These relatives themselves were free of gout. Their serum uric acid concentrations were 6.7, 7.7, and 8.4 mg. per cent, respectively.

The author is indebted to Drs. Walter Bauer, Arlie V. Bock, and Saul Hertz of this clinic for permitting observations on patients from their private practice. Dr. Walter Bauer, and Dr. Harry C. Trimble of the Department of Biological Chemistry, Harvard Medical School, have made many helpful suggestions during the course of the work and in the preparation of the manuscript.

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## "PLATE-LIKE" ATELECTASIS OF THE LUNG\*

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THE clinical importance of atelectatic conditions of the lung and their proper roentgenological recognition has recently been emphasized. Attention has been called to the frequent occurrence of atelectasis in tuberculosis,<sup>1</sup> in bronchiectasis,<sup>2, 3, 4</sup> in minor upper respiratory infections.<sup>5</sup> Usually the collapse of a whole lobe or nearly a whole lobe has been described. The so-called basal triangular shadow as evidence of lower lobe collapse, the triangular shadow at the apex in atelectasis of the upper lobe, as well as the appearance of the collapsed middle lobe have been described in detail by numerous writers.<sup>6, 7, 8, 9, 10</sup> In addition to the characteristic form of the dense shadow cast by the collapsed lobe, the presence of a mediastinal shift is generally considered to be a valuable sign in the differential diagnosis of atelectasis.<sup>11</sup> In partial collapse, the mediastinal shift may be completely absent, but the displacement of the interlobar septum towards the diseased lobe is helpful in making a diagnosis.<sup>10, 12</sup> The smallest localized areas of atelectasis which occur, due to obstruction of a bronchus of the second or third division, do not, however, produce any shift of the interlobar septum. The term generally used to describe small atelectatic areas is that of "patchy atelectasis." Patchy atelectasis is supposed to be indistinguishable from bronchopneumonic infiltration.<sup>13</sup>

Recently, Fleischner<sup>12</sup> has convincingly shown that small areas of pure atelectasis without complicating secondary changes of the parenchyma, are represented by "plate-like" shadows in the lung, which appear as horizontal stripes in both postero-anterior and lateral views. Previously, such horizontal stripes frequently have been mistaken for fibrinous deposits on the pleura.<sup>14</sup> Fleischner observed these stripes associated with three groups of conditions:

1. Abdominal diseases.

In this first group of diseases the horizontal shadow stripes had been observed by other authors previously to Fleischner,<sup>14, 15, 16</sup> and had been interpreted as being due to pleurisy.

2. After contusions of the chest.

3. Associated with minor upper respiratory infections.

Fleischner, by autopsy controls, demonstrated that these plate-like shadows were due to small atelectatic areas. It seemed to us that a further

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proof could be offered by observing the development of these shadows during the reëxpansion of a lobar infectious atelectasis. In infectious atelectasis a previously normal lobe collapses and often reëxpands before severe

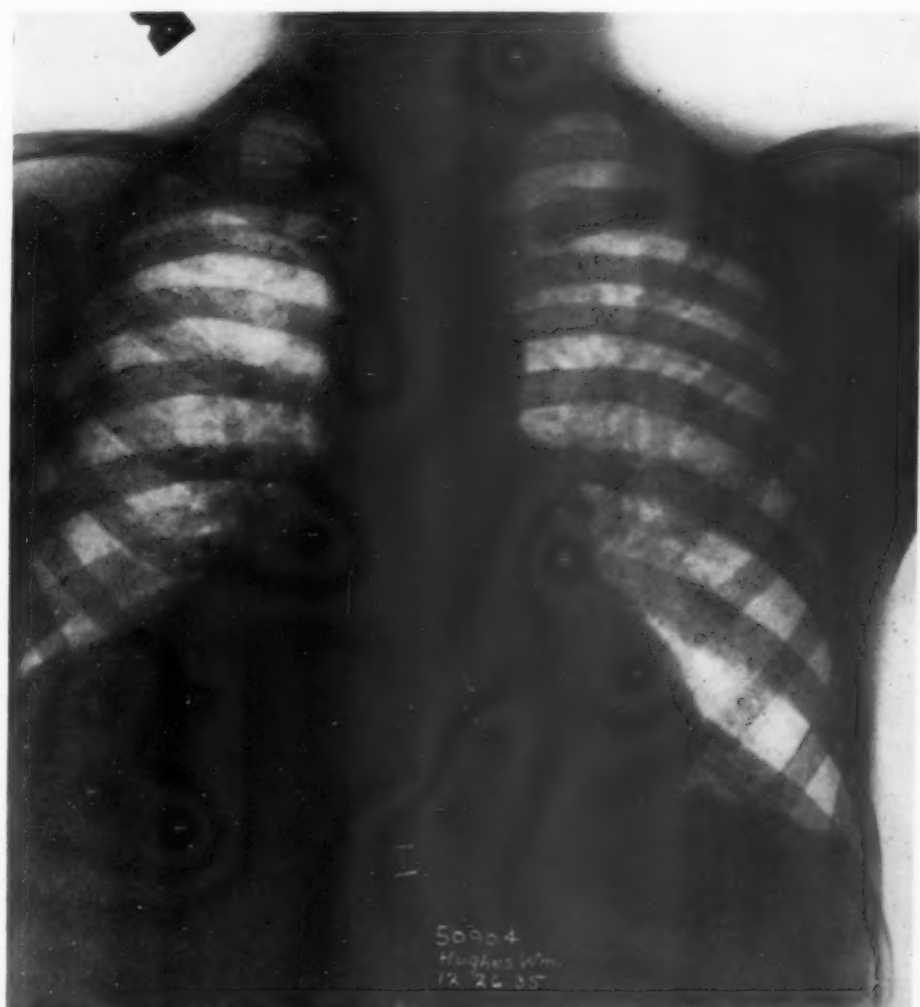


FIG. 1. P. A. view. Dec. 24, 1935. Triangular shadow at the base of the right lung field merging with the shadow of the heart and the right diaphragm. Typical appearance of collapse of the right lower lobe.

chronic changes, such as bronchiectasis or fibrosis, develop.<sup>5,17</sup> It has been shown that the collapse in these cases is not to be explained by a gross plugging of a main bronchus, but by the presence of tenacious sputum in numerous smaller sized bronchi. During the stage of reëxpansion, a few smaller-sized bronchi may remain plugged longer than others. The small atelectatic pulmonary areas supplied by these bronchioli should be demon-

strable at this stage as horizontal shadow stripes. We have seen that this occurs. In a number of cases of typical acute lobar collapse in children due to upper respiratory infection, the horizontal shadow stripes appeared on the



FIG. 1a. Lateral view. Dec. 24, 1935. Note collapsed right lower lobe as a dense shadow overlying the spine.

roentgen-ray film during the stage of re-inflation. They represented at this time the only abnormal finding. Clinically, the health of the patient seemed to be fully restored. The following case may be reported as an example:

#### CASE REPORT

*Case 1.* (I am indebted to the Boston Floating Hospital for the case history.) W. H., a nine year old boy, was admitted to the Boston Floating Hosoiatal on

December 23, 1935, because of fever and anorexia of 10 days' duration. He had suffered from measles at the age of six, and whooping cough at four. Since the whooping cough the boy had frequent attacks of cough and fever during the winter.

On admission, there was rapid breathing and cough. The examination showed



FIG. 2. P. A. view. Oct. 5, 1936. Collapse of the right and the left lower lobes.

limitation of expansion on the right side and dullness posteriorly from apex to base. The breath sounds were diminished and expiration prolonged over this area. The temperature was 101° on admission and terminated by crisis one day later. It stayed normal thereafter.

Films taken one day after admission showed a typical triangular shadow at the right base indicating total collapse of the right lower lobe. There was also some mottling in the left lower lung field behind the heart (figures 1 and 1a).

The patient gradually improved and was discharged on January 16, 1936, to

a recreation home. Roentgen-ray examinations were not repeated at the time of discharge. It was intended to introduce lipiodol into the right lower lobe at a later date, to determine whether or not bronchiectases were present. This seemed advisable because of the present conception that bronchiectasis may develop in cases of spontaneous lobar atelectasis.<sup>18, 4, 7, 5</sup>

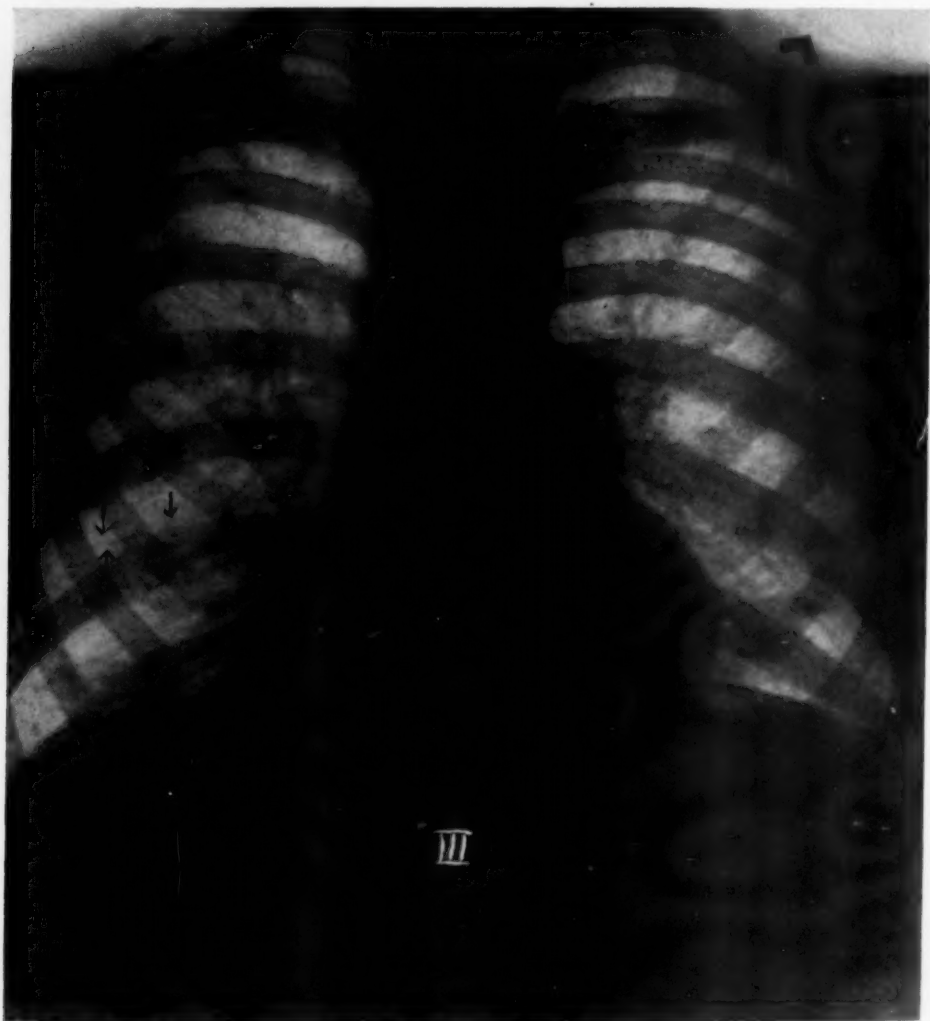


FIG. 3. P. A. view. Nov. 2, 1936. The right lower lobe has partially reexpanded. Indefinite cloudiness in the right cardio-diaphragmatic angle. Arrows indicate the displaced interlobar septum.

In March 1936, three months later, chest films were again taken and showed the right lung to be entirely normal. The previously collapsed right lower lobe had completely reexpanded.

On September 27, 1936, nine months after the original episode, the patient was re-admitted to the Boston Floating Hospital because of fever, cough, shortness of

breath, and pain in the region of the right lower chest of one week's duration. In the interval between March and September, the boy had been well, with the exception of one week's sickness in June, with similar symptoms.

On admission the boy appeared acutely ill, dyspneic, coughing, raising a considerable amount of sputum. Physical findings showed impaired resonance at both bases,



FIG. 4. P. A. view. Nov. 30, 1936. Arrows indicate a horizontal shadow stripe in the right lower lobe, which represents "plate-like" atelectasis.

with diminished breath sounds at the left base. No râles were heard. Tactile fremitus was slightly more pronounced on the right side. The temperature was 103° on admission and dropped to normal at the end of 12 days. Films taken one week after admission (October 5, 1936), while the patient was still acutely ill, showed



collapse of the right and left lower lobes (figure 2). Reëxamination on November 2, 1936, showed marked improvement. There was now partial collapse of the right lower lobe only (figure 3). Clinically, the child had markedly improved in the meantime. The temperature was normal. The cough had disappeared. On November

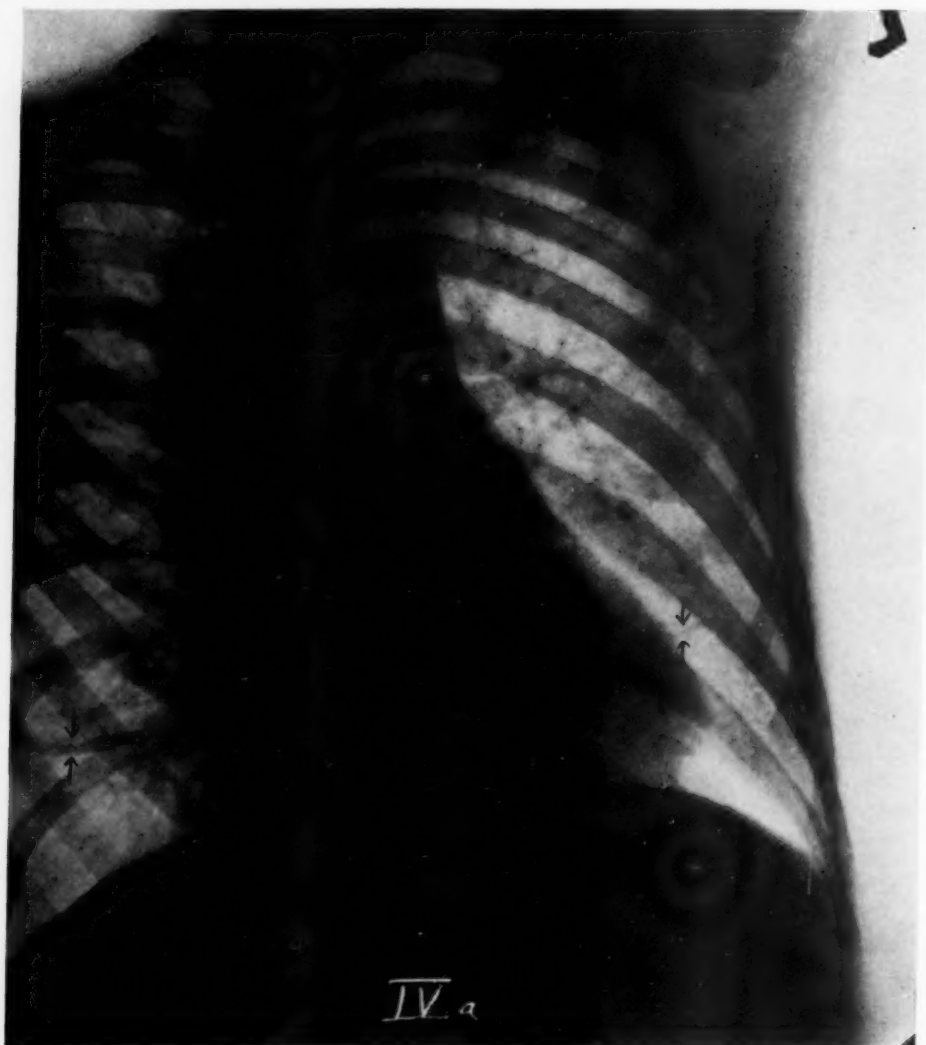


FIG. 4a. Right oblique view. Nov. 30, 1936. Arrows indicate the "plate-like" atelectases. In this view an atelectatic area in the left lower lobe has become visible, which in the P. A. view was hidden behind the heart shadow.

30, 1935, the child appeared clinically well. Films taken at this time showed both diaphragms smooth in outline, freely movable with respiration. There were two transverse shadow stripes in the right lower lung field and one in the left lower lung field.

*Interpretation:* These shadow stripes were considered to represent minute

atelectases due to occlusion of small-sized bronchi in the right and left lower lobes (figures 4 and 4a).

In differential diagnosis, pleural adhesions alone have to be considered. The appearance of the atelectatic areas as thin stripes in both the anterior and lateral films makes it obvious that we are dealing with a plate-like and not with a linear structure. The intrapulmonary origin is therefore evident.

Fleischner explains the appearance of these plate-like shadows by a mechanism which he calls "directed collapse." While in pneumothorax the lung can retract from the lateral chest wall due to the change of pressure within the chest cavity, the conditions for collapse in obstructive atelectasis are fundamentally different. Here, the lung cannot retract from the chest wall. Even if no pleural adhesions are present, the negative pressure acts as an adherent force between the surface of the lung and the chest wall and prevents the collapse of the lung toward the hilus. As there is no possibility for the lung to shrink in a costo-mediastinal direction as in pneumothorax, the tendency of the atelectatic area to diminish in extent can only take place in a crano-caudal direction, perpendicular to the axis of shrinkage in pneumothorax.

#### CONCLUSION

A case of acute lobar collapse due to upper respiratory infection is reported. In the end stage of reexpansion, thin horizontal shadow stripes were seen in the area previously collapsed, and were interpreted as "plate-like" minute areas of atelectases.

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**A COMPARISON OF THE PRESSURES IN ARM  
VEINS AND FEMORAL VEINS WITH  
SPECIAL REFERENCE TO  
CHANGES DURING  
PREGNANCY \***

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KNOWLEDGE of the general level of venous pressure may be usefully applied to the evaluation of cardiac failure and of pericardial obstruction and it may sometimes serve as a guide to the management of these conditions. These applications are widely known and practised. This communication is concerned, not with the general level of venous pressure, but with the study and utilization of local venous pressures in the understanding and description of disease. My colleagues and I were led to make the observations here reported by certain phenomena encountered during our study of pregnant women.<sup>1</sup> During the physical examination of such patients observation was made of an increase in the number and prominence of visible veins over the abdomen, suggesting the development of a collateral circulation. Assuming that collateral venous channels develop in relation to some obstruction to venous blood flow, we undertook a comparison of the pressures in two widely separated portions of the venous system. These were the femoral vein and a vein in the antecubital space. These two points are approximately the same distance from the heart; moreover, one is in the system of the inferior vena cava and distal to the apparent collateral circulation, while the other is in the system of the superior vena cava.

Measurements of venous pressure were made by the direct method described by Moritz and von Tabora.<sup>2</sup> The patient lay on his back in bed and the zero point of the manometer was set at a level 5 cm. dorsal to the fifth costal cartilage. It was found advisable to precede the measurement by a period of rest and to minimize discomfort by the injection of a drop of local anesthetic.

Only some observations by Runge,<sup>3</sup> who compared arm vein pressure with that in veins near the knee, and the study of 11 patients with diverse conditions by Ferris and Wilkins<sup>4</sup> offer information bearing on this point. Therefore, the arm and leg venous pressures were studied in a group of non-pregnant individuals, including normal persons and those with con-

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ditions already known to affect local or general venous pressure. The results of these preliminary observations are summarized in table 1.

TABLE I  
Examples of Venous Pressure in Arm and Leg in Normals and in Patients  
with Various Circulatory Disturbances

		Venous Pressure	
		Arm	Leg
		mm. H <sub>2</sub> O	mm. H <sub>2</sub> O
A.	<i>Normal circulatory system</i>		
	1. Psychoneurosis . . . . .	58	58
B.	<i>Heart disease</i>		
1.	<i>Without failure</i>		
	2. Hypertension (B.P. 210/110) . . . . .	42	41
	(B.P. 212/140) . . . . .	48	55
2.	<i>With failure and without ascites</i>		
	3. Hypertension . . . . .	182	178
3.	<i>With failure and with ascites</i>		
	4. Aortic regurgitation and hypertension . . . . .	238	269
4.	<i>Pericardial obstruction</i>		
	5. Constrictive pericarditis . . . . .	320	304
	6. Pericardial effusion . . . . .	165	167
C.	<i>Mediastinal tumor</i>		
	7. Lymphoma of superior mediastinum . . . . .	360	60
D.	<i>Abdominal tumors</i>		
	8. Fibromyoma of uterus before operation . . . . .	104	274
	Fibromyoma of uterus after operation . . . . .	66	55
E.	<i>Ascites not due to heart disease</i>		
	9. Cirrhosis . . . . .	105	146
	Cirrhosis after removal of 5,000 c.c. . . . .	88	88

In individuals without heart disease or local venous obstruction, the venous pressure is not elevated, and is nearly identical in arm and leg under the conditions of these observations. In patients with heart disease but without congestive failure or pericardial obstruction, the venous pressure is similar in arm and leg and is not elevated. In patients with manifest congestive failure and in those with pericardial obstruction from either fluid or constrictive scar the pressure is elevated. The pressure in such cases is identical (or nearly so) in arm and leg, unless there is a considerable accumulation of fluid in the abdomen. When ascites is present the leg pressure may be higher than the arm pressure. Removal of ascites in such cases results in similar pressures in arm and leg, at a level which is still above normal but often somewhat lower than the original arm pressure.

These impediments to venous flow are central, i.e. they are due to right ventricular failure or to pericardial obstruction and they interfere with the entry of blood into the heart. Obstruction may also be at some peripheral



point, in which case venous pressure may be elevated locally and may differ widely in arm and leg. Examples are given of a patient with a mediastinal tumor in whom the arm pressure is higher than that in the leg, and of patients with intra-abdominal tumor or noncardiac ascites in whom the leg pressure is higher than that in the arm. In some of these patients the collateral circulation led to the visible distention of superficial veins.

TABLE II  
Pressure in the Veins in Arm and Leg of Women During and After Pregnancy

No.	Months of Pregnancy	Venous Pressure		Time after Delivery	Venous Pressure	
		Arm	Leg		Arm	Leg
		mm. H <sub>2</sub> O			mm. H <sub>2</sub> O	
1.	3 months	58	78	6 months	65	70
2.	3½ months	77	100			
	8½ months	56	240	Unknown	108	97
3.	4 months	102	163	5 months	—	118
4.	6½ months	85	154			
	7½ months	98	175			
5.	7 months	156	208			
6.	7 months	102	232			
7.	7½ months	80	145			
8.	8 months	110	201	5 months	—	102
9.	8 months	78	161	4 months	108	92
10.	8 months	102	236	10 days	108	72
11.	8 months	76	200			
12.	8 months	110	215			
13.	8 months	90	170	6 months	30	30
14.	8½ months	51	183	6 months	89	81
15.	8½ months	145	181	7 days	91	87
16.	8½ months	95	220	1 month	110	85
17.	8½ months	138	190	6 weeks	118	97
18.	8½ months	82	188	6 days	162	63
19.	9 months	62	265			
20.	"Near term"	55	178			
21.	"At term"	78	198			
22.	"At term"	82	210			
23.				17 days	48	55

With these observations in mind we may proceed to a consideration of the venous pressures in the arm and leg of pregnant women. Table 2 and figure 1 record observations in 22 women and in every case the leg pressure during pregnancy is notably higher than that in the arm. It is seen that by the fourth month of pregnancy the rise takes place and that it persists and even increases throughout pregnancy. The pressure falls abruptly to normal with delivery.

Similar observations were then made in pregnant bitches. The jugular vein was utilized instead of one at the elbow. It was found that the pressures in the femoral veins of these pregnant animals were higher than those in the jugular veins, and that the difference was comparable to that observed between arm and leg veins in pregnant women. After delivery the dif-

ference was not present. When the pregnant animal's abdomen was opened the femoral venous pressure did not alter, which led us to conclude that the

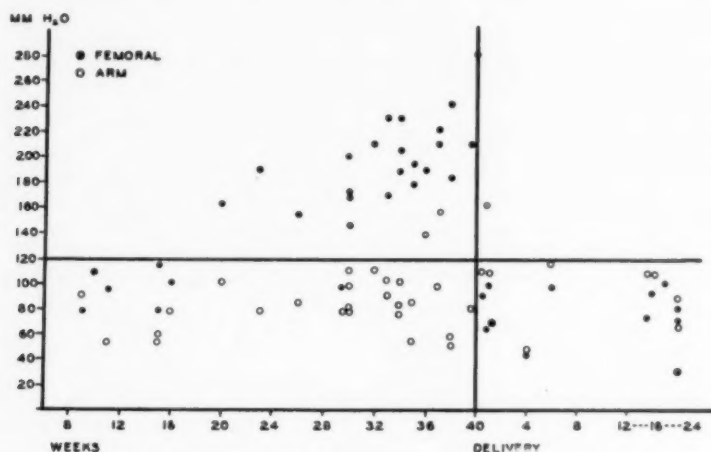


FIG. 1. Venous pressure in pregnancy.

elevated femoral venous pressure was not due to an increase in general intra-abdominal pressure.

Further observations were made concerning the relation of general abdominal pressure and the pressures in the femoral and jugular veins by the injection of salt solution into the peritoneal cavity of dogs. An example of these experiments is shown in table 3. Two points may be noted.

TABLE III

Venous Pressure in Femoral and Jugular Veins in Relation to Elevated Abdominal Pressures in a Dog

C.c. Saline Injected in Peritoneal Cavity	Intra-Abdominal Pressure	Femoral Venous Pressure	Jugular Venous Pressure
	mm. H <sub>2</sub> O	mm. H <sub>2</sub> O	mm. H <sub>2</sub> O
0		-2	-4
300		+6	-3
800	+20	+37	-2
1400	+60	+72	±0
2000	+145	+148	-1
2600	270	270	-1
2800	345	342	+2
3000	410	410	+4
3200	490	495	+11
3300	525	525	+12
All fluid removed from abdomen		0	+8

Note: The scales were set so that the zero point was at the level of the apex beat.

1. The leg venous pressure does not rise until the general abdominal pressure begins to go up.

2. When the leg venous pressure reaches a height comparable to that observed in pregnant women the abdominal wall is tense.

Since the abdominal wall of pregnant women with a high femoral pressure is not tense it is evident that an increase in general abdominal pressure is not the mechanism leading to the elevated femoral pressure in pregnant women.

These observations and those concerned with abdominal tumors suggest that an important factor in the high femoral pressure is the pressure of the gravid uterus upon the veins. This concept is borne out by the following observation in pregnant bitches: When the gravid uterus was lifted from its normal position in the abdomen and supported so that it did not press on the great veins the pressure in the femorals fell, although it still remained above the pressure in the jugulars.

So much for venous obstruction. But the pressure in any vessel is influenced not only by the resistance to outflow but also by the amount and pressure of the blood flowing into it. This point may be illustrated by the situation existing in the veins adjacent to an arteriovenous fistula. In spite of the minimal resistance offered by normal veins the pressure in these vessels is markedly elevated, even some distance away from the fistula.

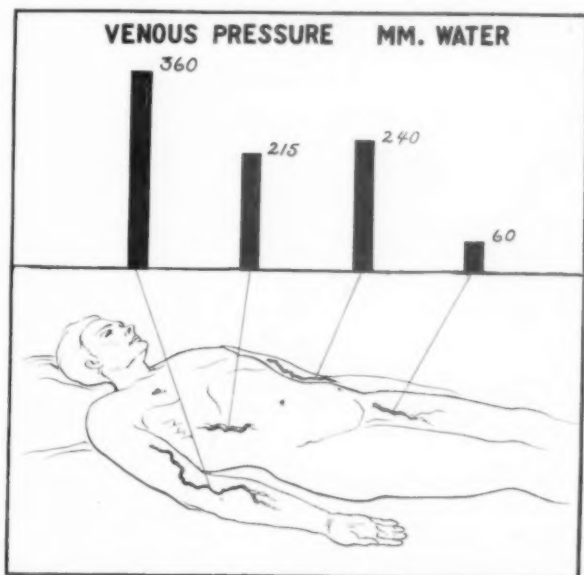


FIG. 2. Venous pressures at various points in a patient with a neoplasm of the superior mediastinum.

There exists evidence that a large volume of blood at a relatively high pressure enters the venous reservoir by way of the placenta. Indeed it may be shown that the maternal placental circulation constitutes a modified arteriovenous fistula. There appears no reason to doubt that the factor of increased inflow is an important cause of the elevated femoral pressure.

The knowledge of venous pressures acquired by these observations may be utilized in the study of conditions other than pregnancy. Two examples may be cited.

The first is a woman of 45 who entered the hospital with a history of increasing dyspnea and abdominal enlargement. The general evidence of heart failure was acceptable until it was observed that even after removal of the ascites the femoral venous pressure was higher than the arm (180 mm. as compared to 115 mm.). This led to a search for an obstruction to venous flow, which was subsequently demonstrated to be an intra-abdominal neoplasm riding directly over the inferior vena cava and partially occluding it. There were no physical signs, other than the differential venous pressures, which pointed to a tumor in this location.

The second patient is a man whose venous pressures are indicated in figure 2.

The venous pressures at these different points, even in the presence in this case of an equivocal roentgen-ray, point clearly to an obstruction in the superior mediastinum. Further roentgen-ray examination verified this localization.

We conclude from these observations:

1. Venous collaterals develop when there is a higher venous pressure in one area of the periphery than in another.

2. The high pressures in the femoral veins of pregnant women are brought about by at least two mechanisms:

- (a) The inflow of a large amount of blood via the placenta.

- (b) Obstruction to venous outflow by the gravid uterus.

3. The comparison of venous pressures in different parts of the body is useful in the understanding and description of disease and may on occasion even be applied to its diagnosis.

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## SPLENIC IRRADIATION IN THE TREATMENT OF PURPURA HEMORRHAGICA \*

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OUR experience with splenic irradiation in purpura hemorrhagica is not in agreement with that of Mettier,<sup>1</sup> who states, "Repeated roentgen irradiation over the spleen in suitable doses is an excellent means of increasing the number of circulating blood platelets in patients with idiopathic thrombocytopenic purpura hemorrhagica."

### EARLY RESULTS

The term control of coagulation was used loosely, and still is, by some to include control of bleeding of any type without attempting to isolate that occurring in purpura hemorrhagica. Therefore, many data reported in the literature can not be considered as significant. Costa Storico<sup>2</sup> states that as early as 1912 Triboulet, Weil, and Parof report favorably on the use of splenic irradiation in hemorrhage. Stephan,<sup>3</sup> in 1920, noted the cessation of bleeding following its use and considered the spleen as the central organ of coagulation. He includes in his report the results of Bucky and Guggenheimer. Aubertin, Levy, and Lereboullet,<sup>4</sup> using an irradiation of 200 R over the spleen, reported the control of the bleeding time followed by a platelet increase in a patient with rheumatoid purpura. Schneider,<sup>5</sup> in 1929, reported favorably on the use of this method, but the blood studies are not complete. In 1932 Hippe and Kochmann<sup>6</sup> stated that excellent results in this disease were obtained by Klempere, Goia, and Bignomi and they conclude, "Through our experience we have reached the point not to lose any time with other treatment in the case of severe thrombopenic bleeding, but irradiate the spleen at once." In 1935 Mettier, Stone, and Purviance<sup>7</sup> report on the use of irradiation in eight patients, stating that there was a cessation of bleeding and a prompt and satisfactory rise in platelets. Rudisill<sup>21</sup> reports similar results in seven patients.

Pancoast, Pendergrass, and Fitz-Hugh,<sup>8</sup> in 1925, report that Corey and Mandelstaum were unable to obtain an effect similar to those already described. Hippe and Kochmann<sup>6</sup> state that Korger, Leschke, Wittkower,

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Mandelstaum and Pakozdy completely declined the use of roentgen-ray for the treatment of thrombopenic purpura. Thormann,<sup>9</sup> in 1928, pointed out that Dolbe and Wertheim criticized the use of irradiation of the spleen in this disease and that Kleistadt had no success in treating essential thrombopenic purpura by this method, and that furthermore Passon felt that splenic

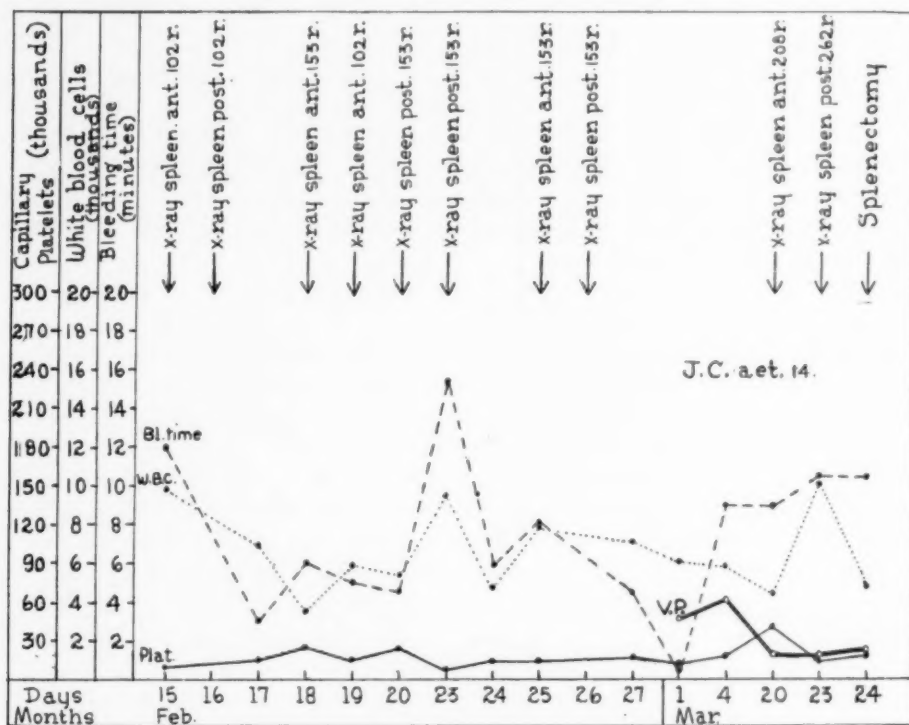


FIG. 1. J. C.: Adequate roentgen-ray to spleen administered from February 15 to March 23. No effect upon platelets or hemorrhagic phenomena. Splenectomy March 24. Patient well in all respects August 11, 1937.

irradiation should not be used in the case of children. Schneider,<sup>5</sup> in 1929, notes that Meda was entirely unsuccessful in treating this disease by this method. Marzullo,<sup>10</sup> in 1933, failed to find any significant clinical improvement in his patients after roentgen-ray therapy, and further states that the platelets did not rise above 100,000. Pancoast, Pendergrass and Fitz-Hugh report their results as inconclusive with this form of treatment, all cases coming to splenectomy.

#### RATIONALE

Two functions of the spleen seem to be well established, (1) the reservoir function, and (2) the destruction of red cells, granulocytes and platelets by the clasmotocytes of endothelial origin in the spleen. One wonders how the cells of the spleen are able to pick out the platelets and destroy them and not destroy the granulocytes and red cells at the same time. We know,

however, that in malignant neutropenia the granulocytes are few in number and the platelets remain at a practically normal level. In hypoplastic anemia and aleukia hemorrhagica both platelets and granulocytes may be reduced to a very low level. This leads us to consider the condition of the bone marrow, in which we find the megakaryocytes normal in number in some purpuric patients and reduced in others. Probably the number of

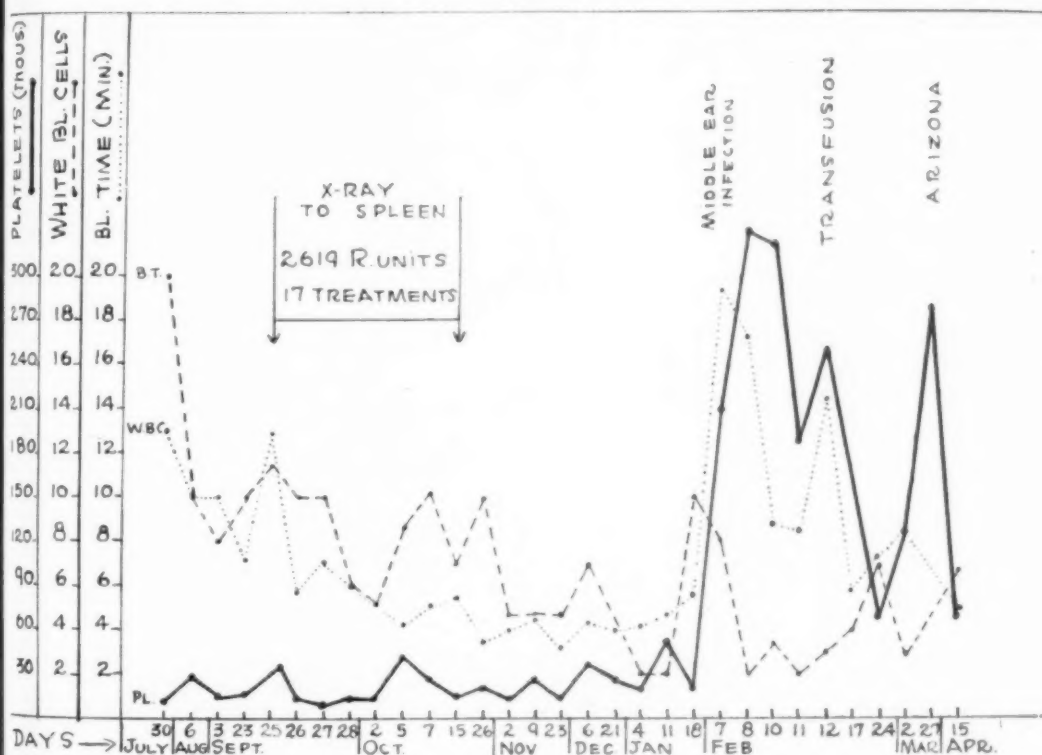


FIG. 2. J. P.: Chronic purpura with acute exacerbations. Roentgen-ray to spleen ineffective. January 1936 developed middle ear disease, mastoiditis, painful and swollen joints, erythema nodosum (purpura rheumatica). Following this the platelets rose to normal, bleeding time fell to normal. Platelets dropped to a low level a month later, rose again while patient was in Arizona. Menstrual cycle established; periods normal. Platelet level at present normal; no hemorrhagic phenomena.

megakaryocytes is not as important as the functional ability of the megakaryocytes that are present in the bone marrow at a given time. More study should be given to the condition of the megakaryocytes as well as to their actual number.

It seems unlikely that the platelet lack in purpura hemorrhagica can be explained purely on the basis of the collection of "hyalin" masses of platelets in thrombosed capillaries, as described by Baehr,<sup>11</sup> if roentgen-ray to the spleen is an effective form of treatment. It may be, however, that depressing or removing splenic function in some way permits some of these

platelets to get back into circulation. Does the spleen have a depressing effect on platelet formation in the bone marrow? This seems unlikely and presumes the presence of a splenic hormone. The importance of anoxemia in bone marrow erythrocytic development is well established and may play

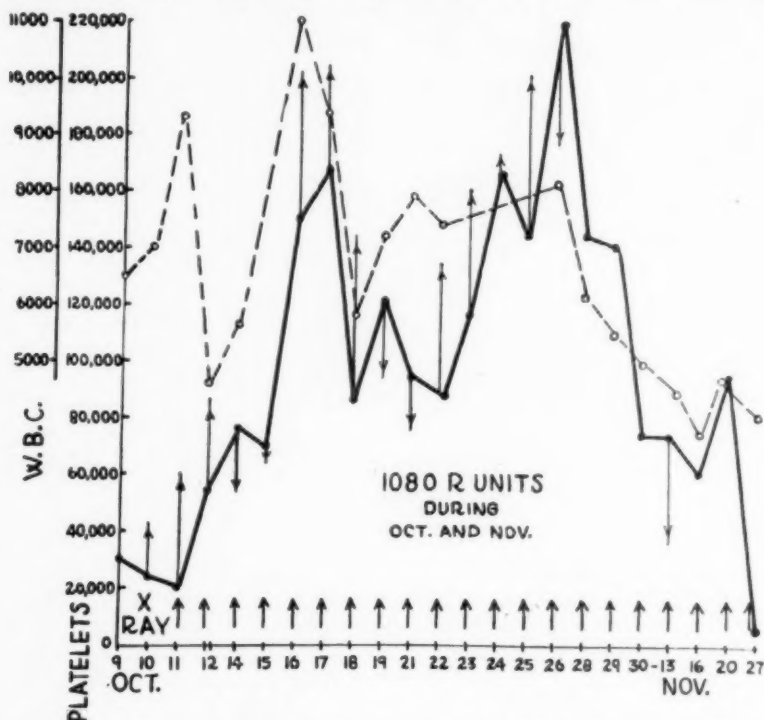


FIG. 3. J. G.: Chronic purpura. Snake venom administered over a three month's period before roentgen-ray treatment to spleen. Following this platelets rose to a high level after the fourth treatment and reached a peak after the fourteenth; then fell to 6,000 per cu. mm. on November 27. Roentgen-ray treatment discontinued because of the accompanying drop of white cells to 2,700. Additional treatment increases total R units to 1620.

a significant part in megakaryocytic activity. Schurer<sup>12</sup> discusses the wide usage of splenic irradiation in treatment of cases of "septic disease," noting favorable results. The dosage is not mentioned, but he concludes that the good effect obtained is due to an outpouring of white blood cells as a result of lymphatic damage or as a result of an irritating effect on the reticulo-endothelial system, thereby increasing the function. We see, therefore, that one group use roentgen-ray to depress the function of the clasmatoocytes and another to stimulate the reticulo-endothelial system, of which the splenic clasmatoocyte is a part. Who is able to determine the dose of roentgen-ray to the spleen which may stimulate in one case and depress in another?

#### EXPERIMENTAL

Using  $\frac{1}{4}$ ,  $\frac{1}{2}$  and 1 erythema dose with filters of 1 Al, 0.3 Cu, 5 Al and 2 Al in rabbits and injecting 1 c.c. of iron oxide intravenously, Schus-

terowna<sup>13</sup> concludes that the cells of the reticulo-endothelial system in the spleen were less able to absorb iron and, therefore, possess less phagocytic ability. Cosati,<sup>14</sup> using 100 R to the exteriorized spleen at 13 cm. with slight filtration, failed to find evidence of marked splenic destruction sufficient to endanger gross splenic function. From this work it would seem

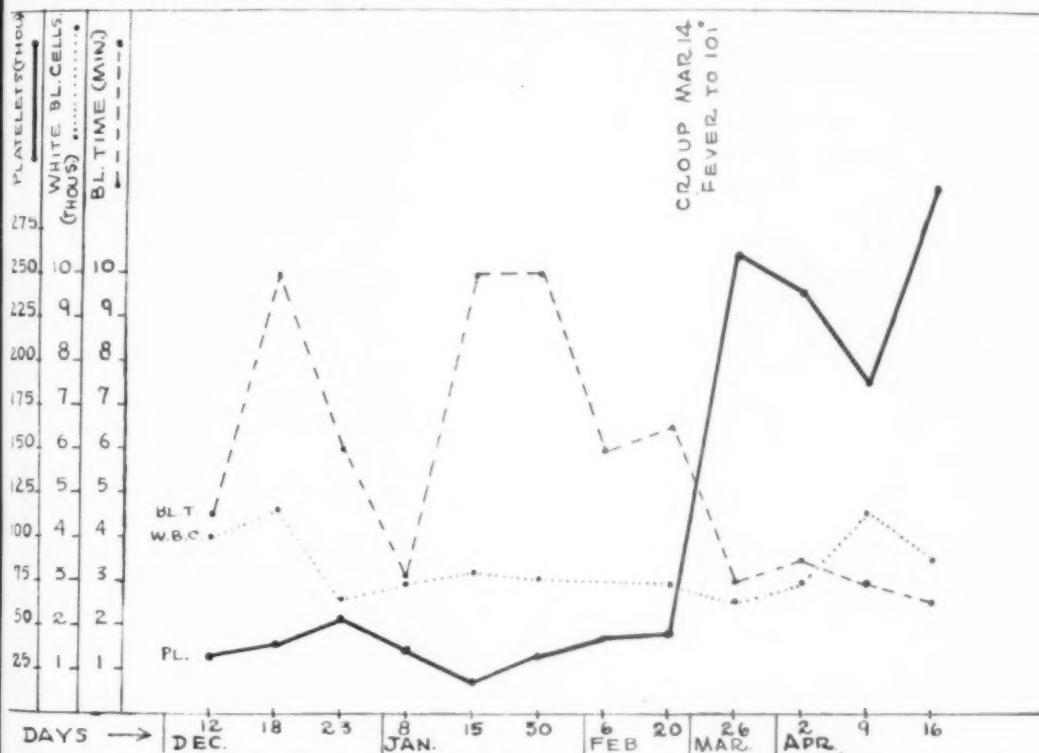


FIG. 4. J. G. (cont'd): Platelets continued at low level until March 14, at which time the child developed croup with temperature rise for a period of 10 days. During this time a platelet rise occurred, which has continued to the present time. The hemorrhagic phenomena also have disappeared.

likely that the so-called roentgen-ray splenectomy is not possible with the doses used in clinical medicine.

#### DOSAGE

Hippe and Kochmann,<sup>6</sup> who employed a dose of from 100 R to 180 R, felt that one should not waste time with other forms of treatment in severe thrombopenic bleeding, but should irradiate the spleen at once. They report a marked increase in blood platelets and a cessation of the hemorrhagic phenomena, and quote Nonta who gave 10 doses of 500 R to a five year old girl with this disease with resultant increase in platelets and cessation of the hemorrhage. Thormann<sup>9</sup> reports the control of hemorrhage in three patients, by means of a dose of 500 R. Costa Storicco, using 100 R to 150 R for two to four doses, reports on the cessation of the hemorrhagic phe-

nomena in two patients. Mettier<sup>7</sup> recommends a dosage of 200 R to 300 R daily until 1,200 R to 3,300 R are given in six to 15 days. One of his patients had a recurrence of the hemorrhagic phenomena and a reduction of platelets, and a second roentgen-ray series was given with similar good results. We note, however, that the patient took the drug Sedormid each time

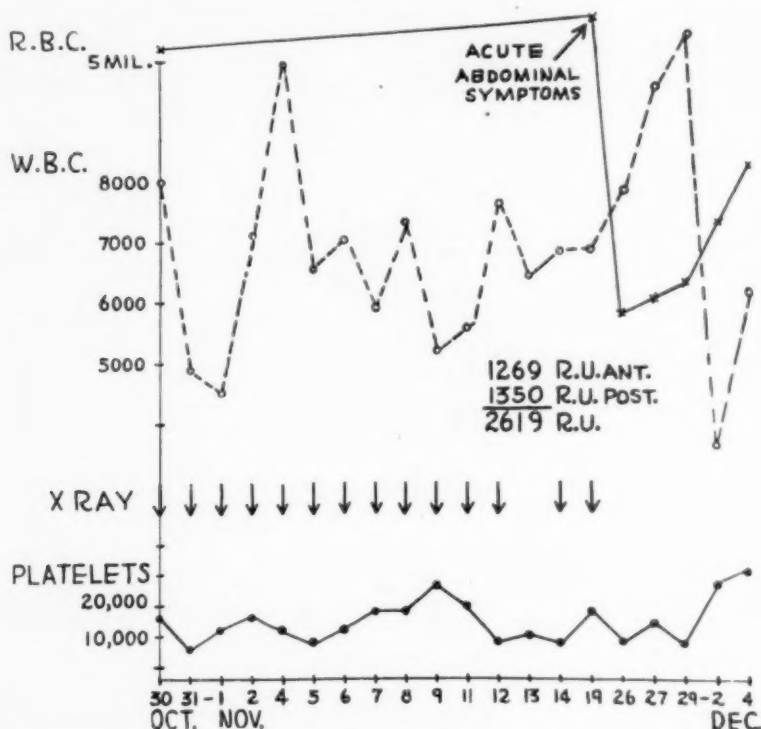


FIG. 5. R. S.: Chronic purpura. Roentgen-ray to spleen ineffective. Acute abdominal pain, marked fall in red cells, and probable intra-abdominal hemorrhage occurred during the treatment. A short time later splenectomy was successfully performed. Additional treatments to spleen not included in chart bring total to 3591 Rn.

before the hemorrhagic phenomena appeared. Pancoast, Pendergrass, and Fitz-Hugh<sup>8</sup> used a dose of approximately 160 R without convincing results.

In our series of 11 patients the dose varied from 54 R to 500 R without the favorable results reported by other observers.

#### EVALUATION OF THERAPEUTIC MEASURES

Amatus Lusitanus<sup>15</sup> described the first case of this disease in 1556, and Willan<sup>16</sup> gave it the name of purpura hemorrhagica in 1801. Many therapeutic measures—purging, bleeding, tincture of iron chloride, injections of whole blood, injections of serum, and others, have been enthusiastically recommended. In the last few years Peck<sup>17</sup> has used snake venom successfully in this disease, but in our hands it has not been efficacious. Anti-



venin has been recommended by Taylor,<sup>18</sup> but we, as well as others, have found it of no value. Congo red intravenously, viosterol by mouth, liver extract by mouth and intramuscularly all have their advocates, but in our experience they have not been helpful.<sup>19</sup> With regard to liver extract, we

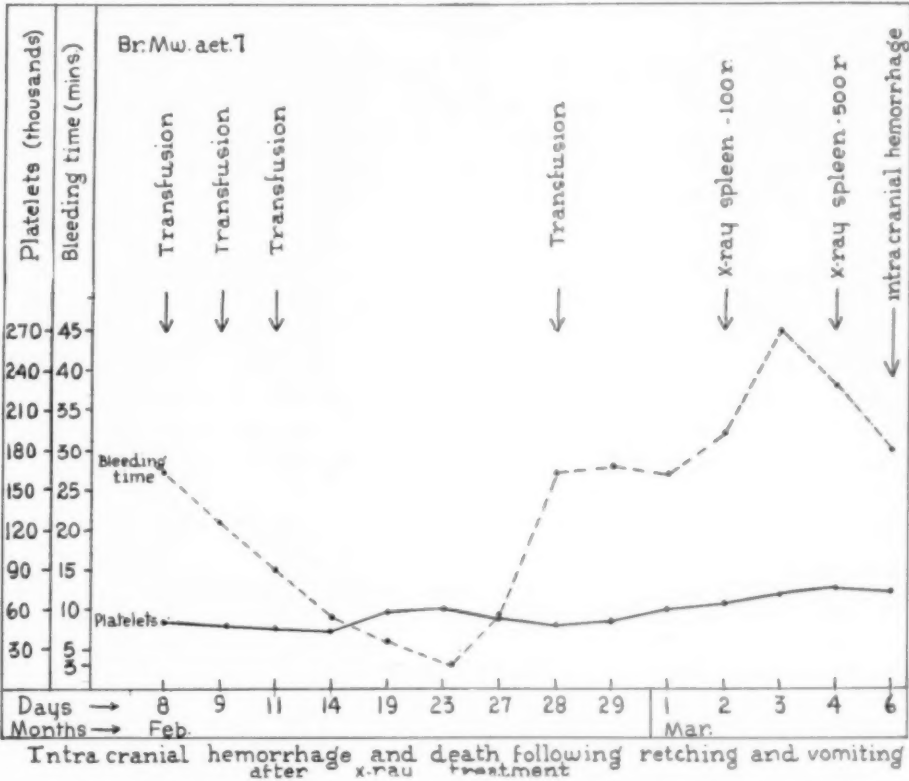


FIG. 6. Br. M. W. Acute purpura treated by transfusion with temporary improvement. March 2, with bleeding time at 32 minutes, roentgen-ray treatment was administered. March 4 a massive dose of roentgen-ray was given, following which retching and vomiting occurred. The patient's face became suffused with petechiae at each spasm; intracranial hemorrhage resulted, followed by death.

have used it in many patients and have failed to get the results reported by others until recently, when one of our patients developed a satisfactory platelet rise after it had been administered for several days. Did the liver extract influence the platelet rise, or was it coincidental? Students of this disease are well aware of the large number of spontaneous cures. In our group, 15 patients are included under this heading. We have knowledge of two patients, one in extremis, who had a sudden cessation of hemorrhagic phenomena and platelet rise after being annointed, and a second who had a similar experience after a visit from a hex doctor. Patients who develop hemorrhagic phenomena and a platelet drop as a result of drug sensitivity frequently have a dramatic increase in platelets after the drug is withdrawn

(Sedormid). As has been pointed out emphatically by Dr. J. H. Pratt,<sup>20</sup> whose experience in this disease is very extensive, one must evaluate all forms of treatment in this disease, with particular consideration of the chance of the coincidental spontaneous cure.

#### CASE REPORTS

In this presentation we report on nine patients who we believe received adequate roentgen-ray therapy and three who received the treatment, but not in sufficient amount to be conclusive. In none of these were we able to obtain favorable results comparable to those reported by other observers.

#### DOSAGE

Our erythema dose is considered to be 800 R measured in air. The equipment delivers approximately 54 R per minute measured in air, using a filter of  $\frac{1}{2}$  mm. of copper, 2 mm. of aluminum. Usually the anterior splenic area is rayed one day and the posterior the next. The following is a brief report of the various patients studied with the result as far as the blood findings are concerned. None of the patients studied had a cessation of hemorrhagic phenomena after roentgen-ray therapy.

#### CASE REPORTS

*Case 1.* C. S., male, aged 3.

Chief Complaint: Spontaneous hematomas, bleeding from nose and ears, petechiae, and ecchymosis.

Family History: Negative.

Past History: Symptoms present since one year of age; otherwise negative except for frequent "colds" and middle ear disease.

Present Illness: One month before admission to the hospital, in 1935, acute hemorrhagic symptoms developed.

Physical Examination: Spleen and liver not enlarged. General systemic examination negative except for conditions mentioned.

#### Blood Studies:

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
4/22/35	94	4.90	8.7	22,000 (Cap.)	9
	Venous clotting time — 4 mins.				
	Roentgen-ray to the spleen anteriorly 153 R.				
4/23/35	90	4.80	5.6	26,000	11
	Roentgen-ray to the spleen posteriorly 153 R.				
4/24/35	92	4.80	4.8	18,000	10+
	Roentgen-ray to the spleen anteriorly 200 R.				
4/25/35	82	4.76	5.8	10,000	9+
	Roentgen-ray to the spleen posteriorly 200 R.				
4/26/35	84	4.51	4.2	12,000	10+
4/27/35	Hemorrhagic phenomena more marked; transfusions and other forms of treatment instituted; roentgen-ray discontinued.				
8/1/35	88	4.39	8.0	24,000	10+

Diagnosis: Chronic purpura hemorrhagica with acute exacerbation. Not benefited by roentgen-ray therapy.

Case 2. E. E., male, aged 12.

Chief Complaint: Epistaxis, petechiae, and ecchymosis for three years.

Family History: Negative.

Past History: Negative.

Admitted October 30, 1935.

Physical Examination: Petechiae and ecchymosis on face, arms and legs. Liver and spleen not palpable.

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
10/29/35	86	5.56	5.2	40,000	4
10/30/35	Roentgen-ray to the spleen anteriorly 108 R.				
	After roentgen-ray to the spleen.				
			5.3	20,000	2½
10/31/35	Before roentgen-ray to the spleen.				
	95	5.24	5.7	16,000	1½
	Roentgen-ray to the spleen posteriorly 108 R.				
	After roentgen-ray to the spleen.				
			4.8	18,000	2½
11/1/35	Before roentgen-ray to the spleen.				
	103	5.51	3.2	12,000	7
	Roentgen-ray to the spleen anteriorly 180 R.				
11/2/35	Before roentgen-ray to the spleen.				
	98	5.69	5.3	18,000	3½
	Roentgen-ray to the spleen anteriorly 108 R.				
	Roentgen-ray to the spleen posteriorly 108 R.				
11/5/35	Roentgen-ray to the spleen anteriorly 108 R.				
	Roentgen-ray to the spleen posteriorly 108 R.				
11/6/35	Roentgen-ray to the spleen anteriorly 108 R.				
	Roentgen-ray to the spleen posteriorly 108 R.				
11/9/35	Before roentgen-ray to the spleen.				
	105	6.03	3.5	20,000	2½
	Roentgen-ray to the spleen posteriorly 108 R.				
	After roentgen-ray to the spleen.				
			6.1	14,000	2
11/13/35	Roentgen-ray to the spleen anteriorly 108 R.				
11/14/35	Before roentgen-ray to the spleen.				
	100	5.73	5.9	20,000	4
	Roentgen-ray to the spleen posteriorly 108 R.				
	After roentgen-ray to the spleen.				
			4.8	6,000	1½
11/16/37	98	6.005	4.2	26,000	2
	Roentgen-ray to the spleen anteriorly 108 R.				
11/19/35	102	5.41	4.4	10,000	5½
	Roentgen-ray to the spleen posteriorly 108 R.				
11/21/35	104	5.62	3.8	38,000	6
	Roentgen-ray to the spleen anteriorly 108 R.				
	Roentgen-ray to the spleen posteriorly 108 R.				
11/23/35			4.3	8,000	10
	Roentgen-ray to the spleen anteriorly 108 R.				
	Roentgen-ray to the spleen posteriorly 108 R.				
11/26/35			4.2	18,000	7
	Roentgen-ray to the spleen anteriorly 108 R.				
	Roentgen-ray to the spleen posteriorly 108 R.				
12/3/35			4.0	24,000	2½
	Roentgen-ray to the spleen anteriorly 108 R.				
	Roentgen-ray to the spleen posteriorly 108 R.				
	After roentgen-ray to the spleen.				
			6.4	38,000	4
12/5/35	89	4.91	5.6	16,000	6
12/19/35	96	5.37	6.3	24,000	3
5/25/36	96	5.002	2.8	18,000	12

Diagnosis: Chronic purpura hemorrhagica. Roentgen-ray treatment ineffective.

*Case 3.* J. M., male, aged 10.

Chief Complaint: Bruising, nose bleed.

Family History: Negative.

Past History: Measles, easy bruising in 1932. Patient states that he had nose bleed at the change of seasons. The hemorrhage was so severe at times that he became unconscious. He states that he does not bruise unless he injures himself.

Admitted May 18, 1937.

Blood Studies:

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
5/18/37	79	4.45	8.7	34,000 (Cap.) 58,000 (Ven.)	10+
	Venous clotting time—5.				
5/19/37	82	5.13	8.1	34,000 (Cap.)	10+
	Roentgen-ray to the spleen anteriorly 200 R.				
5/20/37	Roentgen-ray to the spleen posteriorly 200 R.				
5/21/37	95	5.21	8.8	40,000 (Cap.) 42,000 (Ven.)	6½
	Roentgen-ray to the spleen anteriorly 250 R.				
5/22/37	104	5.13	6.1	50,000 (Cap.)	3½
5/24/37	81	4.50	4.9	8,000 (Cap.) 14,000 (Ven.)	10+
	Roentgen-ray to the spleen anteriorly 250 R.				
5/25/37	83	4.07	4.8	12,000 (Cap.) 14,000 (Ven.)	10+
	Roentgen-ray to the spleen posteriorly 300 R.				
5/26/37	88	4.44	5.0	16,000 (Cap.) 22,000 (Ven.)	10+
5/29/37	87	4.74	4.0	20,000 (Cap.) 20,000 (Ven.)	2½
8/9/37	85	4.80	8.6	21,000 (Cap.) 24,000 (Ven.)	10+

Diagnosis: Chronic purpura hemorrhagica with acute exacerbation. Roentgen-ray treatment ineffective for control of hemorrhagic phenomena and increase in platelets.

*Case 4.* J. C., male, aged 14.

Chief Complaint: Bleeding from nose, petechiae, and ecchymosis (general).

Family History: Negative.

Past History: Chicken pox and measles. In 1928 patient was hospitalized because of repeated nose bleed. The nose bleed, petechiae and ecchymoses continued at various intervals until 1936, when patient was admitted to another hospital, at which time the blood loss from the nose was unusually severe following a cold. There was some bleeding from the gums at this time.

Present Illness: On admission, February 15, 1937, the patient had been bleeding from the nose for some days. There was marked ecchymosis of the arms and legs and bleeding from the gums. The spleen was palpable, the liver not felt.

Blood Studies: See chart.

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
2/15/37	71	3.45	9.9	10,000	12
	Roentgen-ray to the spleen anteriorly 102 R.				
2/16/37					
	Roentgen-ray to the spleen posteriorly 102 R.				
2/17/37	46	2.40	7.0	16,000	3
	Roentgen-ray to the spleen anteriorly 153 R.				
2/18/37	43	2.63	3.6	26,000	6
	Roentgen-ray to the spleen anteriorly 102 R.				
2/19/37	37	2.18	5.8	16,000	5
	Roentgen-ray to the spleen posteriorly 153 R.				
2/20/37	38	2.27	5.4	26,000	4½
	Roentgen-ray to the spleen posteriorly 153 R.				
2/23/37	52	2.87	9.5	8,000	15
	Roentgen-ray to the spleen anteriorly 153 R.				
2/25/37	53	2.81	7.8	16,000	8
	Roentgen-ray to the spleen posteriorly 153 R.				
2/26/37	46	2.49	7.2	18,000	4½
2/27/37	40	2.84	6.2	12,000 (Cap.)	½
3/1/37				46,000 (Ven.)	
				20,000 (Cap.)	
3/4/37	45	2.68	5.8	61,000 (Ven.)	9
	Roentgen-ray to the spleen anteriorly 208 R.				
3/20/37	64	3.17	4.0	6,000 (Cap.)	
				21,000 (Ven.)	10+
	Roentgen-ray to the spleen posteriorly 262 R.				
3/23/37	70	3.72	4.1	22,000 (Cap.)	
				26,000 (Ven.)	
3/24/37	Splenectomy				

Diagnosis: Chronic purpura hemorrhagica with acute exacerbation. Roentgen-ray treatment ineffective.

Case 5. R. C., male, aged 7.

Chief Complaint: Weakness, bleeding from gums, ecchymoses, and petechiae.

Family History: Negative.

Past History: Measles, pertussis, pneumonia, frequent attacks of tonsillitis. Tonsillectomy two years previously; no excessive bleeding.

Present Illness: Admitted June 1, 1926. Patient, bleeding extensively from gums, fell in the street and was brought to the hospital.

Physical Examination: Gums oozing, legs and thighs covered with ecchymoses and petechiae. Spleen is palpable, liver not felt.

July 16, after treatment with transfusions, roentgen-ray therapy was administered in a dose of approximately 540 R. Unfortunately no platelet counts are available on this day. The last platelet count recorded was on June 23, at which time the platelets were 88,000. On June 21 the hemoglobin was 88 per cent red blood cells 4,700,000, white blood cells 6,400, platelets 334,000.

The patient was improving continually at the time of roentgen-ray. Hemorrhagic phenomena had disappeared and the platelets were increasing. In our opinion there was no indication for roentgen-ray therapy, nor was there indication for splenectomy, which was performed on the 28th of July. The patient died November 23, 1926, during a re-admission to the hospital, when a diagnosis of osteomyelitis and broncho-pneumonia was made.



*Case 6.* J. D., male, aged 53.

Chief Complaint: Epistaxis.

Family History: Negative.

Past History: Smallpox at 5, bruised easily for the past 8 or 9 years.

Present Illness: November 1933 spontaneous nose bleed. Admitted to the hospital January 27, 1934. A cold in the head brought on a severe hemorrhage January 26. On admission purpuric spots were present in the mouth and the extremities and there was bleeding from both nasal passages. Various forms of treatment were used—transfusion, liver extract, snake venom, and others.

Blood Studies:

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
3/19/34	80	4.20	8.6	16,000	10+
3/20/34	Roentgen-ray to the spleen anteriorly 108 R.				
3/21/34	80	4.20	7.2	16,000	10+
3/22/34	Roentgen-ray to the spleen anteriorly 162 R.				
3/23/34	84	4.42	8.2	20,000	10+
3/26/34	Roentgen-ray to the spleen anteriorly 162 R.				
3/27/34	85	4.60	5.6	18,000	10+
3/28/34	Roentgen-ray to the spleen posteriorly 108 R.				
3/29/34	80	4.16	4.8	10,000	10+
3/30/34	Roentgen-ray to the spleen posteriorly 162 R.				
3/31/34	80	4.30	4.0	16,000	10+
4/2/34	82	4.70	4.8	15,000	10+

Diagnosis: Chronic purpura hemorrhagica with acute exacerbation. Roentgen-ray treatment ineffective.

*Case 7.* P. S., female, aged 45.

Admitted March 1921, in extremis, bleeding from mucous membranes, nose, mouth, vagina. Ecchymoses and petechiae were present.

Her hemoglobin was 30 per cent, red blood cells 2,000,000, white blood cells 8,600, platelets 16,000. Roentgen-ray was administered over the spleen in a dose of 500 R, but she died in 48 hours, although transfusions were used.

*Case 8.* R. S., female, aged 23.

Chief Complaint: Bleeding from nose and gums since age 6, excessive menstruation since age 14, tendency to bruise easily since age 6, long bleeding from cuts since age 6, weakness, dyspnea and palpation, and swelling of ankles for three years.

Family History: Negative.

Past History: Measles, pertussis, frequent headaches, tendency to head colds. Tonsils treated by electro-coagulation six years ago.

Present Illness: Admitted Oct. 1935. Frequent spontaneous nose bleed since age of 6, occurring daily until onset of menses, then about one every two weeks, lasting one to two hours. At age of 20 the nose bleed occurred once a month. Spontaneous bleeding from the gums since age 21. Fourteen teeth have been extracted in the last two years, bled two to four days after each extraction.

Physical Examination: Spleen slightly enlarged, liver not palpable. Petechiae and ecchymoses present on lower extremities. Some tenderness in right lower quadrant.

Roentgen-ray treatments daily from October 30 to November 12, except Sundays. Seven anterior spleen 216 R; one 162 R; one 108 R; one 135 R. Seven posterior spleen; five at 216 R; one at 162 R; one at 108 R. One lateral spleen at 108 R; one left and right lateral chest 108 R each.

Blood Studies: See chart.

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
10/14/35		5.09		16,000	3½
10/30/35		Before roentgen-ray to the spleen.			
	76	5.12	7.5	16,000	7½
		After roentgen-ray to the spleen.			
				18,000	10+
10/31/35		Before roentgen-ray to the spleen.			
	76	5.03	4.9	6,000	10+
		After roentgen-ray to the spleen.			
				14,000	9½
11/1/35		Before roentgen-ray to the spleen.			
	70	4.71	4.5	12,000	5
		After roentgen-ray to the spleen.			
				10,000	9½
11/2/35		Before roentgen-ray to the spleen.			
	80	5.30	7.1	16,000	1½
		After roentgen-ray to the spleen.			
				18,000	15+
11/4/35		Before roentgen-ray to the spleen.			
		5.10	9.9	12,000	10+
		After roentgen-ray to the spleen.			
				18,000	4
11/5/35		Before roentgen-ray to the spleen.			
			6.5	8,000	3½
11/6/35		Before roentgen-ray to the spleen.			
		5.35	7.1	12,000	10+
		After roentgen-ray to the spleen.			
				24,000	8½
11/7/35		Before roentgen-ray to the spleen.			
	81	5.44	5.8	18,000	8
		After roentgen-ray to the spleen.			
				12,000	6½
11/8/35		Before roentgen-ray to the spleen.			
		5.45	7.3	18,000	8½
11/9/35		After roentgen-ray to the spleen.			
		4.71	5.2	26,000	4½
11/11/35		Before roentgen-ray to the spleen.			
			5.6	20,000	2
		After roentgen-ray to the spleen.			
				12,000	6
11/12/35		Before roentgen-ray to the spleen.			
			7.6	8,000	10+
11/13/35		Before roentgen-ray to the spleen.			
		5.21	6.4	10,000	5½
11/14/35		Before roentgen-ray to the spleen.			
		5.07	6.8	8,000	7½
		After roentgen-ray to the spleen.			
				16,000	10+
11/19/35		5.28	6.8	18,000	7½
11/26/35	47	2.97	7.8	8,000	9½
11/30/35	53	3.01	6.8		
12/4/35	64	4.13	6.1		
12/9/35	60	3.49	4.9	6,000	10+
12/20/35		Before roentgen-ray to the spleen.			
	70	4.79	6.1	16,000	10+
		After roentgen-ray to the spleen.			
				22,000	
12/21/35		Before roentgen-ray to the spleen.			
		4.70	5.5	16,000	
		After roentgen-ray to the spleen.			
				16,000	7½
12/23/35		Before roentgen-ray to the spleen.			
		3.79	4.1	16,000	4½

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
After roentgen-ray to the spleen.					
1/2/36		5.01	6.3	10,000	6½
2/4/36		4.45		24,000	10+
2/10/36	52	4.09	5.6	14,000	9
2/11/36	52	4.09	3.9	25,000	20
Splenectomy 3:30 p.m.					
After splenectomy—5:00 p.m.					
	62	4.54	19.9	68,000	15
2/12/36	52	3.61	44.0	378,000	1
2/13/36	46	3.18	24.0	722,000	15
2/14/36	48	3.43	12.7	886,000	2½
2/15/36	52	3.69	12.1	1,320,000	3½
2/17/36	53	4.02		2,366,000	1½
2/21/36	50	3.18	7.6	2,120,000	3
2/26/36		3.50		1,620,000	15
3/3/36	55	3.75		464,000	3½
3/9/36	51	3.54	6.0	292,000	1
3/13/36		4.00		222,000	1
3/26/36	51	3.53	8.0	366,000	½
4/8/36	68	4.76	6.4	251,000	1½

Diagnosis: Chronic purpura hemorrhagica. Roentgen-ray treatment ineffective.

Comment: On October 19, following roentgen-ray to the spleen, the patient developed acute abdominal pain associated with marked fall in red cells of more than 2,000,000 per cubic mm. There was distinct abdominal tenderness, rise in temperature, and an increase in the white cell count above her usual level. The differential count showed a decided shift to the left. We felt that she may have had an intra-abdominal hemorrhage as there was evidence of free fluid in the abdominal cavity. The roentgen-ray treatments were discontinued.

Case 9. J. G., female, aged four.

Chief Complaint: Easy bruising, nose bleed.

Family History: Negative.

Past History: Always healthy until present illness.

Present Illness: Admitted October 1935. At two years of age child had severe infection involving nose, throat, and sinuses. This condition was present for four or five weeks. Since then she has bruised easily, has had many head colds with frequent nose bleed and one profuse hemorrhage from bowel.

Physical Examination: Bruises and petechiae present on the arms, lower extremities and the body. Spleen and liver are both palpable, although not materially enlarged.

Blood Studies: See charts 3 and 4.

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
10/9/35	73	4.63	6.5	30,000	4
10/10/35	Before roentgen-ray to the spleen.				
	79		7.0	24,000	3½
10/11/35	Roentgen-ray to the spleen anteriorly and posteriorly 108 R.				
	After roentgen-ray to the spleen.				
	73	4.12	7.8	32,000	3½
10/12/36	Roentgen-ray to the spleen anteriorly and posteriorly 108 R.				
	Before roentgen-ray to the spleen.				
	75	4.41	9.3	20,000	5
	After roentgen-ray to the spleen.				
				60,000	3½
10/14/35	Before roentgen-ray to the spleen.				
	80	4.65	4.6	54,000	4
	After roentgen-ray to the spleen.				
			5.9	86,000	10+

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
10/15/35	Before roentgen-ray to the spleen.				
	97	4.52	5.6	72,000	3
	After roentgen-ray to the spleen.			54,000	12+
10/16/35	Before roentgen-ray to the spleen.				
		5.08	3.8	70,000	2
	After roentgen-ray to the spleen.			64,000	10+
10/17/35	Before roentgen-ray to the spleen.				
	84	4.93	16.7	152,000	3
	After roentgen-ray to the spleen			206,000	
10/18/35	Before roentgen-ray to the spleen.				
	86	4.70	9.4	168,000	2½
	After roentgen-ray to the spleen.			126,000	2
10/19/35	Before roentgen-ray to the spleen.				
		4.96	6.8	86,000	7½
	After roentgen-ray to the spleen.			144,000	5½
10/21/35	Before roentgen-ray to the spleen.				
		4.17	8.2	120,000	4
	After roentgen-ray to the spleen.			94,000	10+
10/22/35	Before roentgen-ray to the spleen.				
	81	4.81	8.9	94,000	3
	After roentgen-ray to the spleen.			76,000	10
10/23/35	Before roentgen-ray to the spleen.				
	82	5.19	8.4	88,000	6
	After roentgen-ray to the spleen.			134,000	3½
10/24/35	Before roentgen-ray to the spleen.				
	80	5.53	8.3	116,000	5
	After roentgen-ray to the spleen.			160,000	3
10/25/35	Before roentgen-ray to the spleen.				
		5.60	9.1	168,000	3
	After roentgen-ray to the spleen.			172,000	5½
10/26/35	Before roentgen-ray to the spleen.				
	80	4.53	7.2	144,000	5½
	After roentgen-ray to the spleen.			200,000	1
10/28/37	Before roentgen-ray to the spleen.				
	75	4.77	9.4	218,000	2
	After roentgen-ray to the spleen.			176,000	2½
10/29/35	Before roentgen-ray to the spleen.				
	83	4.09	8.8	144,000	5
10/30/35	Roentgen-ray anteriorly and posteriorly 108 R.				
	Before roentgen-ray to the spleen.				
		4.13	6.1	140,000	5½
11/9/35	After roentgen-ray to the spleen.			142,000	½
	Roentgen-ray anteriorly and posteriorly 108 R.				
	Before roentgen-ray to the spleen.			74,000	6
11/13/35	Roentgen-ray anteriorly and posteriorly 108 R.				
	Before roentgen-ray to the spleen.			74,000	5½
	After roentgen-ray to the spleen.			13,000	5
11/16/35	Roentgen-ray anteriorly and posteriorly 108 R.				
	Before roentgen-ray to the spleen.			60,000	3½
	After roentgen-ray to the spleen.			60,000	3½

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
11/20/35	Roentgen-ray anteriorly and posteriorly 108 R. Before roentgen-ray to the spleen.				
		4.11	4.7	94,000	5
	After roentgen-ray to the spleen.				
			3.5	84,000	2
11/27/35	Roentgen-ray anteriorly and posteriorly 108 R. Before roentgen-ray to the spleen.				
		4.31	4.0	6,000	7
	After roentgen-ray to the spleen.				
			3.4	6,000	4
12/12/35	75	3.72	2.7	32,000	4½
12/18/35		3.66	4.6	38,000	10
12/23/35		4.24	2.6	54,000	6
1/15/36		4.52	3.3	18,000	10
2/20/36		4.74	2.9	46,000	6½
Croup March 14, 1936. Fever to 101°. Sick 10 days.					
3/26/36		4.27	2.6	260,000	3
4/2/36	83	4.44	3.0	238,000	3½
4/9/36		5.11	4.6	188,000	3
4/16/36	80	3.91	3.5	292,000	2½
4/30/36				206,000	
5/8/36	77	3.86	2.9	188,000	3
5/12/36	76	4.22	3.3	174,000	
3 injections of liver extract.					
5/26/36		5.14	4.0	252,000	2½

Thirty roentgen-ray treatments to the spleen anteriorly and posteriorly, total 1,620 R.

The rise in blood platelets which occurred from October 14 to October 17 was followed by a drop from that date until October 23, at which time they rose to a high point of 218,000 on the 28th of October. From this time on, in spite of roentgen-ray treatment, the platelets fell to a low level of 6,000 on November 27. The white blood cells also dropped to a level of 2,700, and it was decided to discontinue roentgen-ray therapy. It seemed at that time that the roentgen-ray was bringing about a rise in blood platelets and the roentgen-ray treatment was discontinued from the 30th of October until November 9. From that time on there was no favorable effect from the use of roentgen-ray.

It would seem to us that this patient should be included along with the others as roentgen-ray treatment ineffective. Possibly a more optimistic observer might include this one patient under the heading of "questionable roentgen-ray effect."

*Case 10.* E. S., male, aged 7.

Chief Complaint: Recurrent nose bleed for five months.

Family History: Negative.

Past History: Pertussis, mumps, varicella, pneumonia.

Present Illness: Admitted March 1936. Began to bruise easily at 5 years of age. The summer of 1935 he was in another hospital and was transfused repeatedly. Since September 1935 has had slight attacks of nose bleed, but in the last two weeks he had 6 severe attacks, one on the morning of admission.

Physical Examination: There is bleeding from the left nasal passage anteriorly and posteriorly. Tonsils are large and seem to be infected. Spleen and liver are not felt. Petechiae and ecchymosis are present.



## Blood Studies:

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
3/30/36	32	2.59	16.0	10,000	15+
	Venous clotting time normal.				
	Transfusion 120 c.c.				
3/31/36	38	2.45	9.6	28,000	15+
4/1/36	39	2.27	9.2	22,000	
	Transfusion 120 c.c.				
	After transfusion.				
	44	2.84	12.3	22,000	15+
4/2/36	42	2.92	8.5	32,000	15+
4/4/36	45	3.07	10.2	32,000	
4/6/36		2.26	8.7	14,000	
	Occasional giant platelet seen.				
4/7/36	51	3.10	10.3	6,000	12+
	Transfusion 120 c.c.				
	After transfusion.				
	54	3.14		18,000	15+
4/9/36	54	3.44	6.7	10,000	
	Transfusion 120 c.c.				
	After transfusion.				
	60	3.72	8.2	26,000	10+
4/11/36	Transfusion 120 c.c.				
	After transfusion.				
	60	4.02	7.7	4,000	15+
4/14/36	58	3.91	11.0	28,000	15+
4/15/36	Transfusion 120 c.c.				
	After transfusion.				
	70	4.00	12.6	10,000	15+
4/17/36	63	4.03	8.3	8,000	Long
	Roentgen-ray anterior spleen 108 R.				
	Roentgen-ray posterior spleen 108 R.				
4/18/36	Transfusion 120 c.c., different donor.				
	After transfusion.				
	71	4.23	9.2	20,000	
4/20/36	69	4.78	7.2	8,000	15+
	Roentgen-ray anterior spleen 108 R.				
	Roentgen-ray posterior spleen 108 R.				
4/21/36	Transfusion 120 c.c.				
	After transfusion.				
	77	4.81	6.3	14,000	6½
	Roentgen-ray anterior spleen 108 R.				
	Roentgen-ray posterior spleen 108 R.				
4/22/36	72	4.37	6.2	8,000	15+
4/23/36	76	5.19	7.0	8,000	15+
4/24/36	72	4.24	5.6	26,000	8½
	Roentgen-ray anterior spleen 108 R.				
4/27/36	72	4.65	5.4	10,000	15+
4/29/36	60	3.40	5.4	8,000	Prolonged
	Roentgen-ray anterior spleen 135 R.				
	Roentgen-ray posterior spleen 135 R.				
5/1/36	53	3.07	3.5	8,000	15+
5/2/36	60	3.34	6.8	8,000	10+
	Transfusion.				
5/4/36	62	3.54	7.1	6,000	15+
	Transfusion.				
5/6/36	65	3.56	6.9	22,000	
5/9/36	Transfusion.				
	After transfusion.				
	70	3.60	4.7	16,000	10+

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
5/11/36	70	4.24	5.1	26,000	Prolonged
	Snake venom.				
5/12/36	72	4.00	3.1	2,000	10
	Transfusion.				
5/13/36	73	3.93	3.7	8,000	7
	Snake venom.				
5/15/36	Transfusion.				
	After transfusion.				
	73	4.78	4.8	10,000	15+
5/18/36	67	3.74	5.6	18,000	15+
	Snake venom.				
5/19/36		3.32	5.5	12,000	9
5/22/36	Transfusion.				
	After transfusion.				
	70	3.90	5.3	10,000	15+
6/1/36	71	4.26	6.1	48,000	10+
6/3/36	66	3.38	5.8	12,000	15+
6/5/36	62	3.33	3.9	36,000	15+
6/6/36	61	3.34	4.1	18,000	15+
	Transfusion.				
	Snake venom.				
6/8/36	63	3.97	8.1	6,000	10½
	Transfusion.				
6/11/36	73	3.82	4.2	24,000	15+

Roentgen-ray treatment ineffective with regard to control of hemorrhagic phenomena and platelet increase.

Diagnosis: Chronic purpura hemorrhagica with acute exacerbation.

*Case 11.* J. P., female, aged 12.

Chief Complaint: Easy bruising, nose bleed.

Family History: Negative.

Past History: German measles, mumps, tonsils and adenoids removed at age 7, no excessive bleeding. Patient admitted September 1935. The first evidence of this disease occurred June 1935; petechiae were present on both ankles. Easy bruising had been present two or three weeks previous. Patient treated in another hospital by transfusions, injections of whole blood, and intramuscular injection of pentnucleotide.

Physical Examination: This examination revealed the presence of petechiae, ecchymoses; spleen and liver not enlarged.

Blood Studies: See chart.

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
7/30/35	80	4.84	13.0	8,000	20
8/6/35	77	4.35	10.0	24,000	10
9/3/35	84	4.38	10.9	12,000	8
9/23/35	80	4.25	7.1	14,000	10
9/25/35	85	4.19	12.9	None seen	11½
	Beginning of roentgen-ray treatments to spleen.				
	After	4.11		34,000	5
9/26/35	Before roentgen-ray treatment to the spleen.				
	78	4.45	5.7	8,000	6½
	After roentgen-ray treatment to the spleen.				
		4.10		12,000	10
9/27/35	Before roentgen-ray treatment to the spleen.				
	80	4.09	7.0	8,000	10
9/28/35	Before roentgen-ray treatment to the spleen.				
		4.15	6.0	6,000	4
	After roentgen-ray treatment to the spleen.				
				12,000	6
10/2/35	Before roentgen-ray treatment to the spleen.				
	85	4.42	5.0	52,000	10
	After roentgen-ray treatment to the spleen.				
				12,000	5

Date	Hgb.	R.B.C.	W.B.C.	Platelets	B.T. (mins.)
10/5/35	Before roentgen-ray treatment to the spleen.				
	75	4.53	4.2	48,000	9
	After roentgen-ray treatment to the spleen.				
10/7/35				40,000	8½
	Before roentgen-ray treatment to the spleen.				
	76	4.54	5.1	22,000	4½
10/15/35	After roentgen-ray treatment to the spleen.				
				28,000	10+
	Before roentgen-ray treatment to the spleen.				
10/26/35	78	4.20	5.5	10,000	5
	After roentgen-ray treatment to the spleen.				
				14,000	7
11/2/35	75	4.53	3.5	20,000	10
11/9/35		3.28	4.0	12,000	4½
11/23/35		4.99	4.5	28,000	4½
12/6/35		4.71	3.2	12,000	4½
12/21/35	88	4.81	4.4	36,000	7
1/4/36		4.50	4.0	28,000	
1/11/36		4.41	4.3	20,000	2
1/18/36		4.25	4.7	52,000	2
		4.68	5.6	22,000	10

Roentgen-ray treatments given daily from September 25, 1935, to October 15, 1935 (except September 29, October 6, 8, and 13) on spleen, alternating every other day from anterior to posterior. Seventeen treatments given. Total of 1,431 R units on anterior and 1,188 R units on posterior.

Diagnosis: Subacute purpura hemorrhagica. Roentgen-ray ineffective.

#### DISCUSSION

It is evident from this study that the response to roentgen-ray in the patients which we present has been ineffective. One might stretch a point and give credit to the roentgen-ray for an increase in platelets in one patient (J. G.), but this platelet increase did not hold and was not continued after further roentgen-ray treatment.

Mettier recommends a dosage of from 200 R to 300 R. It is true that we have not given this dosage to all of our patients. However, other observers have obtained results comparable to those of Mettier with a smaller dose. In many of our patients we have administered large doses, that is, 200 R without favorable response. It seems fair to conclude that we have given roentgen-ray a suitable trial in the patients who came under our direction. The response has been disappointing.

Viewing the subject from a broader standpoint, we draw attention to brilliant reports as to cessation of hemorrhagic phenomena and improvement in the platelet numbers by other observers using various forms of treatment; for example, Herron and MacElroy<sup>19</sup> obtained excellent results using autolyzed liver extract (Squibb) by mouth. In our experience, with one exception, and this result is questionable, we were unable to duplicate their results. We do not doubt the results which Mettier and some others have obtained. We do, however, disagree with the statement that roentgen-ray to the spleen in suitable dosage is a satisfactory method of controlling hemorrhagic phenomena and of increasing the number of blood platelets. We assert that this is an unfortunate statement for it leads the general medica!

public to assume that all cases of idiopathic hemorrhagic purpura will be affected favorably if adequate roentgen-ray dosage is administered to the spleen. It seems probable that there are certain patients with this disease who will respond in a manner such as described by Mettier and others, and that there are other patients with the same disease who will fail to respond to adequate roentgen-ray treatment.

When this paper was read before the Section on Medicine of the College of Physicians of Philadelphia, Dr. Fitz-Hugh, in the discussion, stated that he felt the only satisfactory treatment for this disease was splenectomy. Such a statement is, in our opinion, just as unjustifiable as that which Mettier makes with regard to the use of roentgen-ray. At present there is no single treatment for this disease that is eminently satisfactory. Students of this condition know that many patients who have been splenectomized have recurrences. Our plan of treatment is as follows:

If the patient is not in a dangerous state from loss of blood, we give him an opportunity to recover without any special form of treatment. If there is a considerable anemia or a progressive anemia, small transfusions are used. These are given every two or three days, or at times more often, or in larger doses. Vitamin C intravenously is given in selected cases. Liver extract intramuscularly and by mouth is also used. We intend to continue the use of snake venom and roentgen-ray in sufficient dose in all patients in whom we think it is safe, and finally, when all other measures fail we resort to splenectomy.

We wish to call attention again to the danger of roentgen-ray therapy, as is suggested by the effect which we noted in two of our patients: one, R.S., who had an acute intra-abdominal condition with a sudden drop in red blood cells following roentgen-ray therapy, and second, the patient with a long bleeding time, who developed intracranial hemorrhage and died after roentgen-ray treatment, probably as a result of retching and vomiting (chart 6).

#### CONCLUSIONS

1. Roentgen-ray treatment to the spleen in adequate dosage is not a satisfactory form of treatment in all patients with this disease.
2. Purpura hemorrhagica is a disease in which spontaneous cure is frequently seen.
3. Many forms of treatment have been set forth as efficacious in this disease, but when tried by others have been found to be useless.
4. Patients receiving roentgen-ray therapy may become nauseated and vomit. This increases intracranial pressure and intracranial hemorrhage may result, especially if the bleeding time is long.
5. It seems probable that the patients with this disease may fall into a variety of groups, depending upon their response to various forms of treatment. One observer may be successful with a certain form of treatment in a few patients and another observer may be unsuccessful because he is not treating that particular variety of purpura hemorrhagica.

6. Roentgen-ray therapy in this disease, in dosage as set forth by Metier, should be used in selected cases, with the knowledge that it may not be efficacious in the particular patient under treatment.

7. An estimation of the platelets in venous as well as in cutaneous blood may be of help in explaining some of the discrepancies between bleeding time, hemorrhagic phenomena, and platelet number.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR  
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## THE EFFECTS OF INSULIN HYPOGLYCEMIA UPON THE DIABETIC HEART IN CHILDREN AND YOUTH \*

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### INTRODUCTION

THE possibility that harmful effects upon the heart may be produced in diabetic patients by the use of insulin has rested upon the occasional anginal attack after the administration of insulin to cardiac patients. Transitory changes in the electrocardiogram have been noted after the administration of insulin, suggesting some change in the heart muscle. It must be remembered that the injection of insulin into the body in a sufficient quantity to produce hypoglycemia, brings about changes, varying with the individual, the amount of insulin injected, the state of the counter-regulatory system, and undoubtedly other factors. When the blood sugar reaches a sufficiently low level, an increased output of adrenalin occurs, raising the blood pressure, increasing the pulse rate, stimulating the metabolism and tending to counteract the hypoglycemia by the liberation of glucose from the glycogen in the liver. The possibility that these effects may be dangerous in a patient with a heart seriously damaged by coronary disease has been emphasized disproportionately and little attention drawn to the probability of the generally advantageous effect of insulin properly administered. Whether there is any harmful effect upon the healthy heart is an entirely different question.

In this paper are reported the results of a series of electrocardiograms taken in young patients receiving insulin. Attempts were made to obtain electrocardiograms when the blood sugar was high as well as during a period when the blood sugar was low, but before serious symptoms of insulin shock had occurred. In several of the patients mild insulin reactions did occur a few minutes after the electrocardiogram had been taken (usually between 11:30 a.m. and 12 o'clock noon). The object was not to demonstrate effects produced by serious or extensive hypoglycemia with unconsciousness or convulsions but rather to observe changes, if any, occurring during the rapid reduction of the blood sugar by means of injected insulin.

In addition to these observations upon the electrocardiograms of young patients, one patient is reported who was seen in consultation by the writer after she had received by error an overdose of insulin which proved to be fatal. A complete autopsy was made and the results are here summarized.

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## ELECTROCARDIOGRAPHIC DATA

The patients were 13 males and 12 females, varying in age from seven years to 46 years; only two were over 25 years of age. None of these patients gave a history of rheumatic fever or of any infection usually related to heart disease, nor in any of these cases was there clinical evidence of any cardiac lesion. The duration of diabetes in these cases varied from 0.1 year to 14.2 years.

Electrocardiograms were taken with the three conventional leads and a fifth lead from the cardiac apex to the left leg; these are summarized in table 1.

The electrocardiograms were taken usually after breakfast in the morning and again shortly before noon, except in those instances where only a single record is available. Immediately after the electrocardiograms were taken, determinations of the capillary blood sugar were made. The insulin was administered just before breakfast in doses varying from 20 to 50 units.

The cardiac rate per minute varied from 55 in Case 4111, a male, 46 years of age, to 120 in the case of a 13-year old boy, Case 9769. No striking relationship between the heart rate and the blood sugar values could be seen, probably because no severe insulin reactions occurred. It is notable that in severe insulin hypoglycemia a slow pulse often occurs.

Case 6930, aged 19 years, entered the hospital August 8, 1937, unconscious, in an insulin reaction with a blood sugar of 50 milligrams per 100 c.c. He had taken insulin at 2:00 a.m., risen at 10:30 a.m. in a confused state evidently due to hypoglycemia, taken a second dose of unknown amount and arrived at 2:30 p.m. Even after the injection of 35 c.c. of 50 per cent glucose which raised the blood sugar to 130 milligrams, the pulse rate remained at 62. He fought and struggled with attendants but the pulse remained at 62. However, 30 minutes later, when he suddenly came to normally, the pulse quickly rose to 72. This seemed clearly a bradycardia due to a vagus stimulation associated with the general hypoglycemia effect upon the central nervous system.

The rhythm was slightly irregular in every case except in the three oldest patients, Cases 4568, 14405, and 4111. All younger patients showed a sinus arrhythmia, which was present whether the blood sugar was high or low. Extrasystoles of ventricular origin occurred with some frequency in a girl aged 14 years, Case 14491. The absence of extrasystoles in the remaining curves is notable.

Changes in conduction time were conspicuous by their absence. The P-R interval varied from 0.12 to 0.16 second. In two cases this interval was increased with hypoglycemia and in two cases it was shortened. The Q-R-S time varied from 0.04 to 0.08 second. Slight prolongation was noted in five cases and shortening of the interval in three cases. The S-T time varied from 0.22 second to 0.32 second. In five cases it was slightly prolonged and in three slightly shortened with fall in blood sugar.

The maximal height of the R-wave was found to vary from 5 millimeters in Case 9769, a boy 13 years of age with severe diabetes and a large

TABLE I  
Electrocardiograms with Falling Blood Sugar Values

Case No.	Sex	Age (yrs.)	Dur. of DM	Blood Sugar Values			Rate	P-R		Q-R-S		S-T		R		T				
				Date	%	Hour		Seconds	Seconds	Seconds	Seconds	Max.	Lead	I	II	III	V			
13395	F.	7	1.2	2-27-36 3- 5-36 3- 6-36	0.24 0.04 0.12	11:55 a.m. 11:45 a.m. 9:30 a.m.	90 90 90	0.12 0.14 0.12	0.04 0.05 0.05	0.22 0.24 0.24	17 32 30	V V V	2.5 4.0 4.0	4 4 5	1.5 0.5 1.0	4 3 4	T <sub>1</sub> upright in all. Q absent from II at times. W-form of Q-R-S in III. Depression of S-T in V.			
12820	F.	9	2.0	2-24-36 2-27-36 3- 6-36	0.36 0.28 0.08	12:00 noon 10:20 a.m. 9:25 a.m.	80 82 86	0.14 0.14 0.12	0.04 0.04 0.04	0.28 0.28 0.28	39 28 28	V V V	2 2 3	3 4 4	0.5 1.0 1.0	5 3.5 1.5	T <sub>1</sub> upright and varies from 4-5. Q-R-S has W-form in Lead III (2). Depressed S-T interval in all leads.			
12435	M.	9	2.2	2-24-36 2-27-36	0.07 0.18	11:05 a.m. 9:55 a.m.	100 105	0.12 0.12	0.05 0.06	0.26 0.26	24 28	II V	2 3	3 3	0.5 2.0	3 2	T-wave diphasic in V. T-wave diphasic in V.			
9968	M.	9	4.0	3- 1-35 3- 6-35	0.10 none	11:00 a.m. taken	68 88	0.12 0.12	0.08 0.06	0.28 0.24	14 10	II II	3.5 3.5	4 3	0 0	none none	T <sub>2</sub> flat. Notch in ascending Rs. T <sub>2</sub> flat.			
10920	F.	10	1.6	3- 1-35	0.06	11:20 a.m.	80	0.14	0.06	0.28	15	II	1.5	1.0	0.5	none	T <sub>2</sub> inverted.			
9583	M.	10	6.8	2-24-36 2-27-36	0.07 0.11	11:10 a.m. 10:05 a.m.	88 105	0.18 0.18	0.04 0.04	0.28 0.29	30 33	V V	1.5 2	2 2	0.5 0.5	2.5 2.0	T <sub>2</sub> diphasic. T <sub>2</sub> and T <sub>3</sub> inverted.			
13457	M.	10	2.1	3- 1-35	0.11	11:35 a.m.	82	0.12	0.04	0.24	7	I	2.5	1.5	-1.0	none	T <sub>2</sub> diphasic, T <sub>3</sub> inverted.			
11905	M.	11	2.9	3-18-36 3-24-36 3-28-36	0.12 0.073 0.08	11:00 a.m. 9:30 a.m. 10:10 a.m.	84 60 67	0.13 0.12 0.14	0.06 0.04 0.06	0.32 0.28 0.28	22 21 19	V V V	3.5 2.5 3.5	4 5 5	0 2.0 0.5	2 1 2	(1) Rhythm irregular. Q-R-S has W-form in III, T <sub>2</sub> flat, T <sub>3</sub> upright and diphasic, P <sub>2</sub> inverted. (2) T <sub>1</sub> upright, P <sub>1</sub> inverted. Q-R-S <sub>2</sub> has W-form. (3) P <sub>2</sub> inverted, T <sub>2</sub> upright and diphasic.			
14386	F.	11	0.1	2-24-36 2-27-36	0.08 0.15	11:50 a.m. 9:55 a.m.	67 82	0.16 0.14	0.04 0.04	0.26 0.26	15 24	V V	1.3 1.5	1.0 -0.3	-0.3 -0.3	2 2	T <sub>2</sub> inverted, T <sub>3</sub> upright. T <sub>2</sub> upright. Depression of S-T <sub>2</sub> interval.			
6113	M.	11	8.5	2-24-36 2-27-36 6-12-36	0.08 0.08 0.11	12:50 noon 9:30 a.m. 11:15 a.m.	97 87 83	0.16 0.16 0.18	0.06 0.06 0.08	0.26 0.26 0.28	38 34 25	V V V	4.5 3.5 4.0	3.0 4.0 3.5	-2.0 1.0 -0.2	-1.0 3.0 1.5	T <sub>2</sub> inverted. T <sub>3</sub> upright, P <sub>2</sub> inverted. T <sub>2</sub> inverted, T <sub>3</sub> upright.			
12190	M.	12	9.0	3- 5-36 3- 6-36	0.07 0.07	11:30 a.m. 9:40 a.m.	85 80	0.16 0.16	0.04 0.04	0.26 0.28	34 25	V V	2.0 2.0	2.5 3.0	1.0 1.0	2.0 2.0				

T<sub>5</sub> upright in all.  
Q absent from II at times, W-form of Q-R-S in III.  
Depression of S-T in V.

T<sub>5</sub> upright and varies from 4-5.  
Q-R-S has W-form in Lead III (2).  
Depressed S-T interval in all leads.

T-wave diphasic in V.  
T-wave diphasic in V.

T<sub>5</sub> flat.  
T<sub>5</sub> flat. Notch in ascending R<sub>s</sub>.

T<sub>5</sub> inverted.

T<sub>5</sub> diphasic.  
T<sub>5</sub> and T<sub>5</sub> inverted.

T<sub>5</sub> diphasic, T<sub>5</sub> inverted.

(1) Rhythm irregular. Q-R-S has W-form in III. T<sub>5</sub> flat, T<sub>5</sub> upright and diphasic, P<sub>5</sub> inverted. (2) T<sub>5</sub> upright, P<sub>5</sub> inverted. Q-R-S has W-form. (3) P<sub>5</sub> inverted, T<sub>5</sub> upright and diphasic.

T<sub>5</sub> inverted, T<sub>5</sub> upright.  
T<sub>5</sub> upright. Depression of S-T interval.

T<sub>5</sub> inverted.  
T<sub>5</sub> upright, P<sub>5</sub> inverted.  
T<sub>5</sub> inverted, T<sub>5</sub> upright.

TABLE I—Continued

Case No.	Sex	Age (yrs.)	Blood Sugar Values			Rate	P-R	Q-R-S	S-T	R	T				
			Date	%	Hour						I	II	III	V	
4830	M.	13	3- 1-36	0.07	11:20 a.m.	78	0.16	0.05	0.24	15	2.0	1.5	1.0	none	
9769	M.	13	3- 1-35 3- 6-35	0.06 0.39	11:40 a.m. fasting	120 120	0.12 0.12	0.04 0.04	0.24 0.22	5 64	1.5 1.5	1.5 1.5	0.3 0.3	none none	W-form of Q-R-S in III. W-form of Q-R-S in III.
14491	F.	14	3-24-36 3-26-36	0.06 0.14	11:00 a.m. 9:40 a.m.	95 90	0.14 0.14	0.06 0.04	0.26 0.26	13 22	1.0 1.0	2.0 2.0	0.5 0.5	2.0 0.5	Rhythm regular but for 3 extrasystoles. Extra ventricular systole.
8546	F.	15	2-27-36 3- 5-36	0.34 0.06	4:30 p.m. 11:30 a.m.	80 60	0.18 0.16	0.04 0.04	0.30 0.30	12 14	2.5 3.5	3.0 3.0	1.0 0.5	1.0 -0.5	Notching in descending R <sub>s</sub> . Sl. slurring descending R <sub>s</sub> and R <sub>s</sub> .
4715	F.	15	2-24-36 2-27-36	0.06 0.06	11:00 a.m. 9:20 a.m.	70 81	0.15 0.15	0.04 0.06	0.28 0.28	11 13	3.0 3.0	3.0 3.0	-1.5 -0.5	5 5	T <sub>s</sub> inverted. T <sub>s</sub> inverted.
10778	M.	15	2-24-36 2-27-36	0.19 0.13	11:35 a.m. 9:50 a.m.	90 118	0.12 0.12	0.04 0.06	0.26 0.26	26 33	2.5 2.0	2.0 +1.0	-2.0 -1.5	1.0 1.0	Inverted P and Q-R-S-T in III. Upright T <sub>s</sub> . Inverted P and Q-R-S-T in III.
4568	F.	25	3-17-36 3-24-36	0.39 0.14	fasting 11:00 a.m.	90 78	0.16 0.14	0.06 0.08	0.24 0.28	10 10	2.0 2.0	1.0 1.5	-1.0 -1.0	Flat Flat	Inversion of all complexes in III. Inverted P <sub>s</sub> . Notching of R <sub>s</sub> and slurring R <sub>s</sub> .
14405	F.	30	3-24-36	0.04	11:00 a.m.	60	0.16	0.04	0.32	14	1.0	1.5	0.5	1.5	Q <sub>1</sub> inverted, T <sub>s</sub> upright, P <sub>s</sub> and S inverted.
4111	M.	46	3-14-36 3-20-36	0.062 0.20	12 noon 11:00 a.m.	64 55	0.18 0.16	0.08 0.06	0.34 0.30	13 22	2.5 2.0	2.0 3.0	0.5 1.0	3.5 5.0	T <sub>s</sub> inverted, R <sub>s</sub> low, notched. T <sub>s</sub> inverted, R <sub>s</sub> low, notched.
12125	M.	7	3- 6-36	0.05	9:30 a.m.	100	0.14	0.06	0.22	16	2.5	2.0	Flat	4.5	Upright T <sub>s</sub> .
12852	M.	10	7- 7-36 7- 7-36	0.21 0.28	9:45 a.m. 11:45 a.m.	83 73	0.14 0.14	0.06 0.06	0.28 0.26	7 7	3 4	3.5 4.0	Flat Flat	1 1	W-form complex in III, P <sub>s</sub> inverted. T <sub>s</sub> shallow depression in both.
7878	M.	11	7- 7-36 7- 7-36	0.26 0.08	9:20 a.m. 12:10 noon	91 81	0.14 0.14	0.06 0.06	0.24 0.24	11 16	1.5 2.0	2.5 3.0	0.3 -0.5	1.5 1.5	T <sub>s</sub> upright.
8156	F.	15	7- 6-36 7- 7-36	0.17 0.08	9:45 a.m. 11:35 a.m.	91 91	0.12 0.12	0.06 0.06	0.28 0.28	9 10	2.0 1.5	1.5 1.0	Flat -0.5	1.0 1.5	Inversion of complexes in III, T <sub>s</sub> upright. Inversion of complexes in III, T <sub>s</sub> upright.
14478	F.	16	7- 7-36 7- 7-36	0.19 0.12	10:10 a.m. 11:53 a.m.	78 70	0.14 0.14	0.06 0.04	0.28 0.32	9.5 9.0	1.0 1.0	0.5 1.0	Flat Flat	0.5 Flat	Sl. notching in R <sub>s</sub> . Inverted P <sub>s</sub> . Sl. notching in R <sub>s</sub> . Inverted P <sub>s</sub> .
4804	M.	19	7- 6-36 7- 7-36	0.26 0.13	9:50 a.m. 12 noon	80 73	0.16 0.16	0.06 0.06	0.28 0.28	14 12	2 2	2 1.5	-0.5 -0.5	4 4	Inverted P <sub>s</sub> and P <sub>s</sub> . Inverted P <sub>s</sub> and P <sub>s</sub> .

liver, to 38 millimeters in a boy 11 years of age, Case 6113, also a severe case of long duration. The R-wave was maximal in the fifth lead in 30 records, in the second lead in 13 records and in the first lead in 7 records. Changes in the elevation of the R-wave occurred with changes in the blood sugar in a few instances. In four cases, with the fall of the blood sugar during the action of the insulin, the elevation of the R-wave increased, and in five it was diminished.

The deflection of the Q-wave was measured in four leads. Q-waves were absent in at least one lead in all patients, with two exceptions. Very deep Q-waves were observed in three records of Case 6113, a boy of 11 years, with diabetes of long duration. In Lead V the Q-waves were often of great depth, varying from 0 to 28 millimeters.

The T-waves were upright in all cases in the first two leads. There were no striking changes in the T-wave in the first lead. In the second lead, four cases showed a deflection of 1 millimeter or less in the second lead, T-wave. The T-wave in the third lead was flat in five cases and inverted in nine cases. With a fall in the blood sugar, there was a fall in the height of the T-wave in nine cases, but in three the T-wave increased in amplitude while the blood sugar fell. In eight cases there was no change in the T-wave with a change in the blood sugar.

The T-waves in the fifth lead were upright in 10 cases and flat in two cases. With a falling blood sugar due to insulin, there was a lowering of the T-wave in this lead in five cases; in six cases, no change occurred and in two cases the T-wave rose with the falling blood sugar.

W-forms of the Q-R-S intervals occurred in a number of cases as well as inversion of the T-wave or of the entire complex in the third lead.

Miscellaneous changes may be noted. In Case 13395, a girl seven years of age, as the blood sugar fell a more marked depression of the S-T interval in the fifth lead occurred. The T-wave was upright in all four leads. In Case 11905 a variation in the form of the complexes occurred. The early leads were characterized by a lower R-wave and a higher T-wave than later leads. At this time the blood sugar level was 0.07 per cent. Also, in this curve the T-wave in the third lead varied somewhat, being slightly inverted or diphasic in certain cycles. A slightly depressed S-T interval was noted in Case 12190, while the blood sugar was 0.07 per cent and especially in Case 8156, a girl 15 years of age with severe diabetes. Slight notching in the R-wave of the second lead with slurring of the R-wave in the fifth lead occurred in the record of Case 4568, a girl 25 years of age with uncontrolled diabetes of 14 years' duration.

In summary, it may be said that the electrocardiographic changes noted in these cases are slight and not clearly correlated with the intensity of insulin action as indicated by variations in the blood sugar. This lack of correlation is intensified if one compares the mild degrees of hypoglycemia in this series with the severe and prolonged hypoglycemia of the series



reported by Hadorn<sup>1</sup> and de Chatel and Palisa.<sup>2</sup> Actually the blood may contain no glucose without symptoms therefrom as reported in the review by Marble.<sup>14</sup>

#### ABSENCE OF CARDIAC PATHOLOGY IN FATAL HYPOGLYCEMIA

The effect of a fatal dose of insulin is illustrated in the following case report:

##### CASE REPORT

Miss D., Case 12882, aged 27 years, had been treated with insulin since the onset of diabetes in 1928. On August 9, 1934, she returned to her home from work, behaved queerly, and rapidly became unconscious. During the next 12 hours, 200 units of insulin were given and she had convulsions. At noon on August 10 she was unconscious and cyanotic with irregular gasping respiration, and immediately 40 c.c. of 50 per cent glucose solution were given intravenously. Respiration became regular, cyanosis disappeared and the pulse rate, at first 144, fell almost to normal, but at no time did she regain consciousness. Her muscles were at times in tonic contraction and there was a suggestion of the opisthotonus position. A double Babinski sign was present. The pupils were dilated. All normal tendon reflexes were somewhat exaggerated. Lumbar puncture showed clear fluid with a pressure of 650 mm., a trace of globulin, 30 cells, no sugar was present. The analysis of the spinal fluid was carried out at the New England Deaconess Hospital, using a slight adaptation of the Folin technic for blood sugar determination. Laboratory blood sugar analyses were as follows:

Date	Time	Blood Sugar (%)
August—1934		
10.....	8:00 a.m.	Too low to read
10.....	10:30 a.m.	Too low to read
10.....	12:30 p.m.	Too low to read
10.....	3:30 p.m.	27 mg. in 100 c.c.
11.....	7:00 a.m.	500 mg. in 100 c.c.
	at autopsy	540 mg. in 100 c.c.

##### TREATMENT

She received during 18 hours, 600 grams of glucose in solution intravenously or under the skin. At first it was given in 50 per cent solution, 40 c.c. at a time. Later a cannula was tied into a vein and glucose solution continuously administered. Adrenalin did not help.

During the first 20 hours, no urine was obtained. At the end of this time, 3 ounces were obtained by catheter in which the chloride concentration was 0.2 gram per 100 c.c. During the last 12 hours of her life, the blood sugar was high, and the urine contained much sugar. Bladder urine at autopsy contained 6.8 per cent sugar. She never regained consciousness and died 39 hours after onset of hypoglycemic symptoms.

*Pathologic Report:* The gross appearance of the brain as well as of all other tissues was normal, except for slight edema possibly due to the prolonged administration of glucose solution.

Microscopical examination was negative except for the tissues described below:

*Heart:* Slight edema and some perivascular fibrosis.

*Lung:* Congestion and some edema. Rare polymorphonuclear leukocytes, in alveolar walls together with mononuclear leukocytes in alveoli.

*Spleen:* Moderate congestion.

*Pancreas:* Acinar and duct tissue negative. Islands reduced in number and in size. One or two show hypertrophy of so-called "cobra" type.

*Liver:* Moderate central congestion. Glycogenic vacuolization of a few nuclei in periportal hepatic cells.

*Adrenal:* Moderate lymphocytic infiltration of medulla. Usual distribution of lipid in cortex.

*Kidney:* Moderate congestion. No evidence of glycogenic vacuolization.

*Aorta:* Some swelling of subintimal ground substance with early lipid deposition. Few mononuclear phagocytes present, many of which contain considerable amounts of lipid, others of which apparently had been migrating.

*Brain:* Slight subpial and perivascular edema. Pons negative. Cerebellum negative.

#### DISCUSSION

*Electrocardiographic Changes.* The youthful diabetics of this series receiving small doses of insulin without any serious clinical evidences of hypoglycemia, show some electrocardiographic changes, but these changes are slight, inconstant and of little consequence.

In agreement with our findings are those reported by Hadorn<sup>1</sup> and by de Chatel and Palisa<sup>2</sup> in two series of patients studied during the severe prolonged hypoglycemic states produced by insulin in treating schizophrenia.

(1) Hadorn had an opportunity to make 47 observations upon 31 patients undergoing the hypoglycemia treatment for schizophrenia. At the lowest levels, the blood sugar values reached were under 20 milligrams per 100 c.c. His patients were all between the ages of 20 and 40 years with the exception of five whose ages were from 43 to 54 years. The insulin injections were given intramuscularly, the dose varying between 10 and 200 units. He had no cases of initial hyperglycemia. In 21 of Hadorn's cases the pulse rate increased to 100 and in 11 cases it became slowed to 50. In 10 cases there was no change in the pulse rate. The pulse rate did not seem to run parallel to the degree of lowering of the blood sugar. Often, the increase in heart rate occurred shortly after the insulin injection and not at the time of the hypoglycemia. Many times it also occurred that the increased heart rate did not develop until after the noon-day meal or even after the evening meal. In one case, the tachycardia lasted for several weeks. In a majority of Hadorn's cases slight increase in systolic blood pressure occurred, 10 to 20 millimeters, and usually the diastolic pressure fell. In three experiments the blood pressure rose to levels of 170 to 180. Only exceptionally did disturbances of the rhythm occur. The changes observed by Hadorn in the electrocardiograms of his patients may be summarized as follows:

1. The T-wave was inverted once and the P-R interval became shorter in the cases where the pulse rate rose. In 18 cases the P-Q interval was increased by 1/100 to 1/200 of a second and in eight cases it was shortened. The Q-R-S complex was unchanged in 22 cases, was shortened in six and lengthened by 1/100 second to 3/100 in three cases.

2. The S-T interval was unchanged in 26 cases and in 16 cases there was a depression of the S-T interval. The frequency of this depression of the S-T interval is in contrast to the findings of de Chatel.<sup>2</sup>

3. In only 10 cases was the T-wave unchanged. In 32 cases there was more or less marked lowering of the T-wave.

4. The Q-T interval was lengthened in 32 cases. In six cases a U-wave or a doubling of the T-wave occurred.

The observations made by de Chatel and Palisa<sup>2</sup> were in a series of cases of severe induced hypoglycemia, often with coma and convulsions. In these states the

authors noted occasionally a flattening and a lowering of the T-wave, a broadening of the Q-R-S complex and appearance of a sinus arrhythmia, various extrasystoles, auricular fibrillation, prolongation of the conduction time. Against the theory of glycogen impoverishment is that rabbits' heart muscles even with great doses of insulin do not become more glycogen poor. Further, the electrocardiographic changes are not relieved by the administration of grape sugar and, finally, that they do not appear with spontaneous hypoglycemia. However, certain cases, even after the largest insulin doses, show no electrocardiographic changes in the severest types of hypoglycemic shock, and the others may show only a lowering of the T-wave. As a rule, the changes develop within 45 minutes and last for half an hour to an hour after the cessation of the unconsciousness. They were all quite similar and consisted in the lowering of the T-wave. The thoracic lead from the back to the precordium is exceptionally sensitive and at times shows a complete reversal of the T-wave after insulin whereas de Chatel and Palisa did not observe this phenomenon either in the first, second or third leads. In two of their 19 cases there was a sinus arrhythmia. The changes stand in no quantitative relation with the severity of the insulin shock. Patients who appear restless and cheerful an hour after the insulin injection show the same changes as later when in deep coma with profuse sweating, or finally, up to within 15 minutes after the breaking off of the attack. Some cases, even in deep coma with a low blood sugar, show no electrocardiographic changes whatsoever. They gave their insulin intramuscularly whereas in earlier tests without exception the insulin had been given intravenously.

Possibly the absorption from the muscle tissue might lead to certain changes in the insulin which do not allow so direct an influence upon the heart muscle as if the insulin were given intravenously. They are confident it does not depend on the purity of the insulin because they obtained the changes when insulin first began to be manufactured and they were the same as at present when it is much purer.

Their practical conclusions were:

1. That insulin does not exert on the healthy heart the anticipated harmful action which in general has been accepted; even with very low values of the blood sugar, a normal electrocardiogram could be obtained;
2. That their electrocardiographic studies show that even after months of induced severe hypoglycemic attacks permanent changes are not observable;
3. That all of their observations relate exclusively to patients with completely healthy heart muscle, and they cannot be considered as contradicting in any way results obtained in coronary disease after the administration of insulin.

In 50 per cent of Hadorn's cases, increase in the heart rate occurred and indeed often before the beginning of the hypoglycemia. In general, the view has been held that insulin is a parasympathetic stimulant. There is a difference of opinion on this score. A toxic dose of insulin acts through the central sympathetic chain to produce an out-pouring of adrenalin and so leads to a primary tachycardia. Even before hypoglycemia has occurred, a toxic insulin dose could, therefore, paralyze the vagus even though small doses of insulin might be stimulating. The tachycardias in Hadorn's group seemed to be due to adrenalin stimulation.

Smaller insulin doses may act as vagotropic drugs and may thus bring about the bradycardia which has frequently been observed. No increase in the work of the heart occurs when insulin slows the heart. Indeed, Bodo<sup>12</sup> as well as Visscher and Muller<sup>13</sup> demonstrated with the Starling heart-lung preparation, that insulin had a tonic effect upon the heart, in-

creasing the power of the cardiac fibers without any increase in energy liberation.

In cases where no change in pulse rate has occurred, we have positive and negative compensating chronotropic properties of insulin. That adrenalin is in some cases called forth by insulin is indicated by the fact that the systolic blood pressure rises while the diastolic blood pressure falls, a characteristic of adrenalin action. Secondly, leukopenia with a later increase in the leukocytes has occurred. One author holds that it is not the fall in the blood sugar which determined the symptoms of insulin shock but the strength of the opposing reaction from the adrenalin. Thus, the pounding of the heart, the tremor, and the pressure under the sternum are adrenalin symptoms whereas the hunger, weakness, sweating are the direct results of the hypoglycemia. The blood sugar level may fall to 40 milligrams after 5 units of insulin and yet no symptoms result whereas if it reached the same level with a dose of 40 units the symptoms may be marked. It is noteworthy that our children had practically no symptoms even with blood sugar values as low as 0.04 (40 milligrams) per cent.

A rise in blood pressure occurs only when the blood sugar falls below 60 milligrams, according to one author; but LaBarre and Houssa<sup>3</sup> found that, in animals when the blood sugar fell under 95 milligrams the blood pressure rose due to the secretion of adrenalin.

*Clinical Changes:* Unfavorable effects of insulin have been noted almost exclusively in hearts damaged by coronary disease. Thus, Schönbrunner<sup>4</sup> described a 73 year old diabetic woman with a low  $Q_3$ , in whose electrocardiogram there developed regularly 15 minutes after insulin a negative inversion of the T-waves without simultaneous hypoglycemia. In 1923 at the New England Deaconess Hospital a man who had had angina pectoris for many years, died during the night 11 hours after receiving a dose of only 3 units of insulin. At autopsy, his heart had advanced coronary disease with old areas of infarction. At that time, when insulin was new, the possibility of its having precipitated this fatal attack required frank statement. Gigon,<sup>5</sup> as well as others, has described diabetic patients with severe coronary disease who have died suddenly shortly after receiving insulin. As years have passed, the favorable effects of insulin have become more apparent. The following table shows that diabetics, with fatal coronary disease, live longer, the longer insulin was used.

TABLE II  
Diabetics with Coronary Disease  
The Advancing Age at Death During the Insulin Era

	1923-1926	1927-1929	1930-1932	1933-1935
Average Age at Death . . . . .	60.9	62.7	64.4	68.2
Average Duration of Diabetes . . . . .	11	13	13	15
Number of Cases . . . . .	55	56	94	58

## ANIMAL EXPERIMENTS

In animals negative T-waves have been noted in the electrocardiogram after a dose of insulin as well as changes in the heart rate and in the blood pressure. A direct toxic effect has been described affecting stimulus formation, stimulus conduction, and contractility of the heart muscle during a period of hypoglycemia due to insulin. It has been pointed out, however, that the variation in the T-waves and the level of the blood sugars are not parallel.

Rabbits, when given insulin and killed during hypoglycemia, showed about the same glycogen content as control animals. Both with intramuscular and intravenous injection of insulin they found T-wave depression in the animals. With very small doses of insulin (4 units) Hadorn<sup>1</sup> observed an increase in the height of the T-wave. In one case, however, the blood sugar fell to 21 milligrams without a T-wave change. In one animal, the blood sugar rose after 20 units of insulin and during this period they found an isoelectric T-wave. S-T depression did not occur in his animals. Lengthening of the Q-T interval occurred in the animals. With adrenalin injection into the animals, they show typical depressions of the T-wave, negative T-waves and often these were of the coronary type.

Milles and Smith<sup>6</sup> injected epinephrine into the saphenous vein and the coronary artery and observed electrocardiographic changes. A reduction in the amplitude of the T-waves was found as well as other changes of the T-wave and actual inversion. Deviation of the S-T interval from the isoelectric line occurred as well as extrasystoles and actual ventricular fibrillation.

Douglas, Gelfand, and Shookhoff<sup>7</sup> found that the injection of epinephrine into the muscles of the cat would produce marked displacement of the S-T segment in the electrocardiogram. These S-T changes were abolished by nitroglycerine, and were therefore attributed to coronary spasm. Milles and Smith<sup>6</sup> attributed the changes caused by epinephrine to an increase of the myocardial requirements for oxygen beyond the available supply, with consequent functional anoxemia of the myocardium.

Soskin, Katz and Frisch<sup>8</sup> produced hypoglycemia in animals in various ways and concluded that insulin exerts a specially harmful effect upon the heart regardless of hypoglycemia, a point of view difficult to understand when one remembers that insulin is a natural hormone produced physiologically throughout life.

In summary, the important thing is the question of the T-wave. The changes observed are of short duration, and may be reproduced by injection of adrenalin. Many factors such as anemia, CO poisoning, oxygen lack, general infections as well as digitalis itself cause temporary changes in the T-wave. At present, the balance of evidence indicates that the electrocardiographic changes following insulin injections are probably secondary adrenalin effects and without serious significance, except in the presence of coronary arteriosclerosis.



## INSULIN AND CARDIAC METABOLISM

The effect of insulin upon the respiratory quotient, oxygen consumption in hyperglycemia and in hypoglycemia, glycogen deposit and changes in cardiac muscle during insulin action have been repeatedly studied and the results recently reviewed by Cruickshank.<sup>9</sup> In the isolated heart, in the presence of hyperglycemia, insulin increased the oxidation of sugar and the deposition of glucose as glycogen. When hypoglycemia of severe grade was produced, ordinarily the cardiac glycogen reserve is drawn upon. If the hypoglycemia persists, then the heart utilizes other sources of energy and can survive with no sugar in the blood. During the hypoglycemia the addition of insulin has a protective effect in that even then it causes the deposition of glycogen in the heart muscle.

Using diabetic dogs with experimental coronary occlusions, Himwich, Goldfarb and Nahum<sup>10</sup> studied the cardiac metabolism and found data supporting the use of insulin and glucose. They studied 34 animals. They concluded that the infarcted area lost appreciable quantities of the glycogen which appeared in part as increased amounts of available carbohydrate and of lactic acid. Although the normal heart usually absorbs lactic acid from the blood, after occlusion the heart was found to pour lactic acid into the blood stream, probably due to the reduced oxygen supply to the infarcted area. Glucose was absorbed from the blood both before and after the coronary occlusion. These data again suggest that in diabetic patients, especially, the use of glucose and insulin may be of real value in cases with coronary occlusion. Furthermore, Himwich, Goldfarb and Fazikas<sup>11</sup> found that the heart muscle oxidizes non-fatty substances, that is, carbohydrates, very well.

Actually it must be remembered that the results of insulin hypoglycemia are chiefly dependent upon the degree to which sugar is lost from the blood and the length of time the tissues are without a supply of glucose from the blood. Certain tissues, like the liver, have a store of glucose upon which they can surely subsist. Other tissues, like the central nervous system, can withstand serious hypoglycemia for only a comparatively short time without the development of irreversible changes.

## SUMMARY

1. Electrocardiograms in 25 young diabetics and the record of a fatal case of insulin hypoglycemia are reported.
2. Insulin hypoglycemia has no serious effect upon the normal diabetic heart. Bradycardia is as common as tachycardia.
3. Insulin hypoglycemia may, by reason of its accompanying stimulation of adrenalin secretion, have serious effects upon the heart damaged by coronary disease.
4. Insulin hypoglycemia of sufficient duration will cause irreversible changes in the central nervous system and death.

5. The proper use of insulin and diet in coronary disease complicating diabetes prolongs life.

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## UNILATERAL HEMOGLOBINURIA: ITS OCCURRENCE IN INFARCTION OF THE KIDNEY\*

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HEMOGLOBINURIA is regarded as symptomatic of hemoglobinemia. A small amount of hemoglobin may be free in the blood plasma without appearing in the urine, being taken up and converted to bilirubin by the reticulo-endothelial cells. But the renal threshold for hemoglobin is apparently very low, so that hemoglobinuria is a fairly delicate indicator of hemoglobinemia. Contrary to hemoglobinuria, hematuria is practically always due to a local disorder of the kidneys or urinary passages, though in the so-called essential hematurias the anatomic substratum may be difficult to discover.

In the present note we desire to record briefly three observations showing that this distinction between the significance of hemoglobinuria and that of hematuria, while true in the vast majority of cases, does not invariably hold; occasionally, hemoglobinuria is due to a lesion of the kidney and is then unilateral if the renal affection is one-sided. A few instances of hemoglobinuria caused by renal disease are recorded in the literature. Thus, Bittorf<sup>1</sup> reports three cases of acute glomerulo-nephritis which, after apparently having been cleared up for months, underwent recurrences associated with hemoglobinuria. In each instance the hemoglobinuria appeared after exposure to cold. Since there was no evidence of hemolysis in the blood of an arm vein, the hemoglobin must have been freed in the kidney. He also states that he observed hemoglobinuria, in addition to hematuria, in a case of subacute bacterial endocarditis with embolic focal nephritis. Wagner<sup>2</sup> and Senator<sup>3</sup> also mention hemoglobinuria in the course of acute or chronic Bright's disease. Our observations concern three instances of infarction of the kidney occurring in heart disease.

### CASE REPORTS

*Case 1.* This patient was seen by one of us (E. L.) in consultation in 1919. She was a woman of 55 years who had suffered from mitral stenosis with auricular fibrillation for a number of years. She was suddenly seized with severe, cramp-like pain in the right side of the abdomen. Ovarian or appendicular disease was suspected. The urine at this time did not contain blood. Soon, however, the pain shifted to the left upper abdomen and the left kidney became palpable and tender. The leukocyte count was 32,000 with 82 per cent polymorphonuclears. The bladder urine was acid, contained albumin, a few erythrocytes, and some hyaline and granular casts. Roentgen-ray examination was negative for calculus. Cystoscopy was performed by

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Dr. Leo Buerger. The urine from the right kidney was of normal color and contained albumin and casts and a few erythrocytes but not hemoglobin. The urine from the left side was red and gave a positive guaiac reaction, but no erythrocytes were to be found in the sediment. From the pelvis a large amount of old blood was evacuated. The hemoglobinuria persisted for several days. It then cleared up, as did the abdominal symptoms. There was no recurrence of similar symptoms.

*Case 2.* A woman of 30 years had had rheumatic heart disease since childhood. She presented the classical signs of mitral stenosis. On February 17, 1925 at 12:30 a.m., when feeling comparatively well, she was suddenly seized with severe abdominal cramps, particularly in the right lower quadrant. The pains lasted all night and were not relieved by repeated injections of codein. Unfortunately the urine was not observed during the night.

A specimen of urine obtained at 10 a.m. was acid and intensely red. Very few erythrocytes were found in the sediment after centrifugalization, although numerous hyaline and granular casts were present. The guaiac test was positive. The protein content was 0.31 per cent.

February 18, the urine was very red. The sediment after centrifugalization contained very few erythrocytes, but numerous leukocytes and some hyaline and granular casts were present. The protein content was the same as before. The guaiac test was positive.

February 19, the morning urine was still very red. The guaiac test was positive. The sediment after centrifugalization contained no erythrocytes but numerous granular casts.

The evening urine was also very red and gave a positive guaiac reaction. In the sediment only isolated erythrocytes were seen, and also a few casts and some polymorphonuclear leukocytes. Some of the casts were stained golden by hemoglobin. Large clumps of hemoglobin were present.

Daily examination of the urine from February 20 to 23 revealed continuance of the hemoglobinuria in the absence of hematuria. The hemoglobinuria disappeared on February 24 and did not return.

During the first two days the right kidney (which was ptoed and readily palpable) was very tender; it was not notably enlarged. The tenderness rapidly passed away, and the patient remained with only the symptoms of the preëxisting heart failure. It is of interest to note that one day after the infarction occurred, examination of the blood revealed 29,600 leukocytes per cubic millimeter, 94 per cent of which were polymorphonuclears.

*Case 3.* A woman of 36 years was under observation because of orthopnea and swelling of the feet dating back to the last weeks of a pregnancy which had terminated five months earlier. In a pregnancy 16 years before she had suffered from a pyelitis. On admission to The Mount Sinai Hospital on February 18, 1936, the patient was cyanotic and orthopneic. She had cardiac enlargement, tachycardia, and gallop rhythm. There was engorgement of the lungs and liver and edema of the feet. The blood pressure in the left arm was 170 systolic and 130 diastolic. The pulsations in the right upper extremity were small and the oscillometric excursions diminished. The urine was acid and contained a large amount of protein and scattered erythrocytes and leukocytes. Although the urea nitrogen content of the blood was only 17 mg. per cent, the concentration test revealed severe impairment of renal function; the maximum specific gravity was only 1.012. The roentgenogram revealed a calculus in the right kidney. It was thought that the patient's symptoms were due to heart failure secondary to hypertension and perhaps coronary artery disease. Whether the hypertension was essential in type or the result of a pyelonephritic contracted kidney was not clear.

February 27, the patient was suddenly seized with severe knife-like pain in the left upper quadrant which persisted for about an hour. The skin was cold and

clammy. The pulse was feeble and rapid, the blood pressure unobtainable. The urine was yellow in color. In the sediment of the centrifuged urine, there were 100 to 200 leukocytes and 10 to 20 erythrocytes per high power field.

February 28, she complained of left costovertebral pain radiating to the right upper quadrant. There was shock tenderness in the left costovertebral region. The temperature rose to 101°. There was a leukocytosis of 21,000 with 76 per cent polymorphonuclears.\* Later in the day, the left kidney became palpable and tender. The urine was unchanged in color. There was no increase in the small number of erythrocytes found in the sediment of the centrifuged urine. At this time, the nature of the attack was obscure; the most likely possibilities seemed to be left-sided renal colic of calculous origin (there was known to be a stone in the right kidney) or infarction of the left kidney.

February 29, a specimen of urine was obtained which was burgundy red in color. On centrifuging, there was a small amount of white sediment, but the supernatant fluid remained red and gave a very strongly positive guaiac reaction. Spectroscopic examination of the supernatant fluid disclosed oxyhemoglobin in solution. The sediment contained a moderate number of leukocytes, some of which were clumped, a few hyaline and granular casts, and about 20 erythrocytes per high power field. On the basis of the hemoglobinuria, a diagnosis of infarction of the left kidney was made.

From February 29 to March 2, inclusive, the burgundy red color of the urine due to the presence of dissolved hemoglobin persisted. The sediment of the centrifuged urine contained between 1 and 6 erythrocytes per high power field. The urine obtained on the morning of March 3, the day of death, was yellowish in color but still gave a strongly positive guaiac reaction.

Necropsy revealed recent thrombosis of the right circumflex coronary artery and old occlusion of the left anterior descending branch of the left coronary artery. There was myofibrosis of the anterior and posterior walls of the left ventricle with an aneurysm of the posterior wall. Over areas of fresh myomalacia at the apices of the left and right ventricles were mural thrombi. There was embolic occlusion of the left renal and superior mesenteric arteries. The left renal artery, just beyond its origin, was occluded by a recent blood clot. The left kidney was infarcted in toto, and was largely a dirty brown red in color. The right kidney was the seat of pyelonephritic contraction.

#### COMMENT

It is not immediately obvious why hemoglobinuria should occur in some instances of renal infarction while the large majority present hematuria. The arteries of the kidney are typical end arteries in the sense of Cohnheim and renal infarcts are probably always anemic in their inception. The gray-colored anemic area is usually surrounded by a red border of circulatory stasis and collateral hyperemia, with hemorrhages from dilated capillaries. Microscopic examination of this portion shows the tubules filled with blood coming from the ectatic and ruptured intertubular capillaries. This is the source of the *hematuria* which commonly occurs in infarcts. Hemoglobinuria, however, when it occurs, is probably to be accounted for by a different mechanism. Following the infarction, sufficient blood may reach the infarcted area to make it hemorrhagic. In the autolysis which the infarcted area undergoes, large numbers of erythrocytes are destroyed with liberation of their hemoglobin. Diffusion of the free blood pigment into neighboring

\* High leukocytosis is not at all uncommon in infarction in any organ; it may also occur, as one of us<sup>4</sup> has pointed out, in intracardiac thrombosis not followed by infarction.



patent uriniferous tubules would cause hemoglobinuria. Evidence of such diffusion is found in hemosiderin deposits in the vicinity of old hemorrhagic infarcts. Because of the presence of old blood in the renal pelvis in the first case, the question must be brought up of the possibility of some hemolysis occurring there. It is to be noted that in Case 3, which came to postmortem examination, there was no old blood in the pelvis.

From the above observations, it is evident that hemoglobinuria is not absolutely pathognomonic of hemoglobinemia, for it occurs in connection with embolic infarction of the kidney. In our first case, the clinical picture was that of renal infarction and the hemoglobinuria was proved to be purely unilateral. In Cases 2 and 3 the clinical picture was the same as in Case 1. In Case 3 unilateral infarction was demonstrated at the postmortem examination. There is no reason to doubt that, although ureteral catheterization was not carried out in these two cases, the hemoglobinuria was also unilateral.

Judging by the third case, the phenomenon may well prove to be occasionally of practical diagnostic significance in the differentiation of infarction of the kidney from nephrolithiasis occurring in a patient suffering from cardiac disease. It is evident that studies should be made of separated specimens of urine, by means of ureteral catheterization, in cases of hemoglobinuria, particularly those in which the condition is not manifestly hemoglobinemic in origin.

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**THE PRESENT MORTALITY OF DIABETIC CHILDREN—A REMEDIABLE AND THEREFORE  
HOPEFUL INDEX OF THE FUTURE  
OF THE DIABETIC CHILD\***

By ELLIOTT P. JOSLIN, M.D., F.A.C.P., *Boston, Massachusetts*

WHEN a diabetic child dies today it causes me far more pain than it did half a generation ago. Before the discovery of insulin we did not expect diabetic children to live and if they did, we knew their existence would be as much "labor and sorrow" as for people passing three score years and ten until diabetic coma almost mercifully snatched them away. At that time diabetic children seldom survived a year, but in each quinquennium since, the duration of the fatal cases has nearly doubled, to 2.7 years for 1922-1927, to 4.7 years for 1927-1932, to 9 years for 1932-1937. Today the situation is sharply altered. My own cases show a present mortality of about one per hundred per year, and calculations of the Metropolitan Life Insurance Company based upon the same group indicate that the life expectancy of the diabetic child of 10 years is 31.7 years. I know too that it is possible for a large part of these years to be spent happily and productively. Therefore, for diabetic children to die during the first or second decade of diabetes is truly deplorable.

*Diabetic Coma.* Until the use of insulin, diabetic coma came as a thief in the night and took practically all children. But since we have had insulin, you and I know that the death of a single child from diabetic coma signifies pure and unadulterated neglect and nothing else. Groping in the dark, as we all were prior to insulin, we had reached the stage, nevertheless, when in hospitals coma had almost ceased to originate *sui generis*. When insulin arrived we soon learned that even in actual coma it was the child who by all odds had the best prognosis. In our series treated during coma at the New England Deaconess Hospital there has been 1 death in 83 children under 15 years of age and 3 deaths among 129 patients in coma between 10 and 20 years. At the Children's Hospital in Boston I am told by Dr. Butler that there has been no death in the institution from diabetes from any cause in the last 15 years. Contrast these facts with the report I will now give of the deaths of my diabetic patients with onset in childhood under the age of 15 years since I gave my first dose of insulin on August 7, 1922.

My diabetic children, and I use the word children in the fatherly sense, for once a child always a child to a parent, have numbered 1071 † between

\* Received for publication August 12, 1937.

† One hundred sixty-one children died before insulin was used in this clinic, August 7, 1922.

TABLE I  
 Fatal Results During 15 Years Treatment of 1063 Diabetic Children  
 August 1922-1937  
 The Causes of Death of 104 Diabetic Children

Date	Deaths Coma		Deaths Non-coma									
			Tuber- culosis		Infec- tions		Hypo- glycemia		Acci- dents		Misc.	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
1922-1927 Total 35 Av. Dur. 2.7 yr.	32	91	0	0	3	9	0	0	0	0	0	0
1927-1932 Total 27 Av. Dur. 4.7 yr.	19	70	2	7	3	11	2	8	1	4	0	0
1932-1937 Total 42 Av. Dur. 9 yr.	18	43	7	17	11	26	2	5	1	2	3	7

August 7, 1922 and July 1, 1937. Of these, now scattered literally all over the world, there have come to my attention the deaths of one hundred and four. It is possible there are a very few more, because the complete "follow-up" was over six months ago. Among the causes of death diabetic coma is foremost and despite the relative innocuousness of this complication in childhood at the Children's Hospital and the Deaconess Hospital, just cited, in the first five-year period 1922-1927, 91 per cent of the 35 deaths were attributed to it. In the second five years coma deaths fell to 70 per cent among the 27 deaths, and even in the five years ending now it has caused 43 per cent of the 42 fatalities. This is actually higher than the coma mortality for all my patients of all ages in the eight years prior to insulin when it was only 41.6 per cent. Yet you and I believe a death from diabetic coma to be needless and almost as inexcusable as a death from diphtheria.

What can one do about it? We can reiterate the necessity for insulin both to doctor and patient in season and out of season, and of enough insulin whenever glycosuria exists, particularly in the presence of infections or complications of any sort and we can emphasize attention to the rules I have so often given patients.

A. Never omit insulin unless the urine is sugar free. Keep to your diet and in case of an infection take more insulin if necessary to keep sugar free. It is imperative to test the urine frequently during an acute illness.

B. If you feel sick and especially if you have FEVER, NAUSEA and VOMIT-

ING or even severe pains in the abdomen: 1. Call a doctor. 2. Go to bed. 3. Take a cup of coffee, tea, cocoa shells or broth every hour and live upon acute illness diet (oranges 3, oatmeal, small portion, bread, 3 slices, milk, one quart, 1 egg, little butter). If the urine contains sugar, take regular insulin every hour under your doctor's direction. 4. You need the entire time of a nurse or friend to care for you until you are well. 5. Move the bowels with an enema.

Should we teach a test for acetone or diacetic acid? So far I have hesitated to do so, first for fear the patient would assume too much responsibility and second, because it would simply add to the worries of the diabetic life. Without it the coma mortality for all my patients similarly scattered was but 6.1 per cent for 981 deaths between January 1, 1930 and March 13, 1935.

The patients themselves are fairly innocent of the charge of dying of coma. I am sure you would agree if you read the accounts which I receive. It would hardly do to print them because the laity would not realize that although the coma mortality for childhood cases is shockingly high, the rate of decrease is rapid and during the next five years probably the decline will go on and be accelerated. And my reasons for this belief are that at present patients are taught more about their disease, doctors who are more conversant with insulin are in the saddle, and laboratory facilities, although often still deficient and in many localities unavailable at night and upon holidays and Sundays, are multiplying.

Mobile coma units should be organized for areas without first class laboratories. These might consist of (1) a technician with an outfit for analysis of urine, blood sugar,  $\text{CO}_2$  combining power, non-protein nitrogen and sodium chloride; (2) a nurse and (3) a doctor. The expense for furnishing such an outfit is relatively trifling compared with the cost of a neglected coma case in a hospital and it could operate throughout a radius of 100 miles. It is unlikely that it would need to go many times to the same section, because the benefit which would accrue from it would be so obvious that the community would recognize and provide for the same.

Each diabetic child must always be recognized as a coma possibility and this the patient, the relatives and the family doctor should realize. On this account, I believe there should be in advance a plan for hospital accommodations not only for coma but for all diabetic emergencies. However, discretion must be exercised in giving instruction to patients upon medical subjects and this holds particularly for diabetic coma. It is all right to picture the ease with which diabetic patients go into coma, but for very obvious reasons the disagreeable symptoms attending the process, as well as the discomforts of treatment, should be stressed else in a moment of discouragement patients might deliberately welcome it as a means to an end.

*Pulmonary Tuberculosis.* Tuberculosis does not develop unannounced and it seems a shame that diabetic children who are so intimately in contact with the medical profession should acquire it, much less die of it. In the first quinquennium following Banting's discovery we had no deaths from

tuberculosis and this applies as well to the entire group of children I saw prior to 1922 even as far back as 1898. The reason is plain—children did not live long enough in that period to acquire tuberculosis, or, if they did develop it, death from coma carried them off before tuberculosis became the lethal factor. Later between 1927 and 1932, when the average duration of diabetes for the 27 fatal cases in children had reached 4.7 years, tuberculosis caused two deaths (7 per cent) and in the next five years, 1932–1937, when the duration was nine years, there were seven cases (17 per cent) among the 42 deaths, making a total of nine fatalities from tuberculosis in the last 15 years. I might add that of my five fatal cases in children whose diabetic duration was 15 years or more, there was one death or 20 per cent from tuberculosis and, in fact, of the 10 deaths with a diabetic duration between 10 and 15 years there were four or 40 per cent from tuberculosis. From the above, it is plainly evident how essential it is to look for tuberculosis in diabetic children because it is almost as preventable and as needless as diabetic coma.

The ages, dates of onset of tuberculosis and of diabetes, and dates of deaths are given in table 2. Four of the children were males and five females. We have warned girls especially about tuberculosis because these five included two who had taken up nursing and the tuberculosis followed. Now we say no diabetic girl should become a nurse.

TABLE II  
Nine Instances of Tuberculosis in 104 Deaths of Diabetic Children

Case No.	Sex	Birth Date	Onset				Death	
			Diabetes		Tuberculosis			
			Date	Age	Date	Age	Date	Age
2274	M.	Jan. 1915	Jan. 15, 1921	6.0	Jan. 1927	12.0	Feb. 13, 1934	19.1
3795	F.	May 2, 1910	Dec. 15, 1923	13.0	Jan. 1930	19.7	Mar. 17, 1930	19.8
6957	M.	Jan. 22, 1912	May 10, 1924	12.3	Nov. 1932	20.8	Aug. 10, 1933	21.6
4232	F.	Aug. 21, 1907	Sept. 1921	14.1	Mar. 23, 1928	20.6	Nov. 25, 1936	29.3
4743	F.	June 9, 1908	March, 1923	14.8	Nov. 1931	23.4	May 25, 1936	27.9
5932	M.	June 4, 1913	Feb. 1927	13.7	Jan. 1932	18.6	March 18, 1937	23.8
7041	M.	Jan. 24, 1916	April, 1922	6.3	Feb. 1930	14.1	Oct. 30, 1930	14.8
7047	F.	July 27, 1917	June 5, 1928	10.9	May, 1934	16.8	Jan. 1935	17.5
12385	F.	June 7, 1919	Jan. 1929	9.6	Nov. 1933	14.4	Jan. 9, 1934	14.6

The duration of the diabetes before the onset of the tuberculosis in no instance was less than 4.9 years and it did not exceed 8.6 years. The total duration of the diabetes varied between 5 years and 15.2 years and averaged 9.8 years which is actually greater by 2.4 years than for the 15 cases with onset in childhood dying from all causes in the first decade of life between January 1, 1930, and March 13, 1935, and 3.3 years greater than for the



29 cases with onset in childhood dying in the second decade of life in the same period.

The duration of the tuberculosis from its onset until death varied between 0.1 of a year and 7.1 years. In five of the nine cases, it was less than one year. It is only fair to add, however, that we now have four living children with tuberculosis, and two with tubercle bacilli in the sputum. The tuberculosis has gone on in these living cases from 2.6 to 9.3 years.

The high incidence of tuberculosis in diabetic children was first called to my attention by my colleague, Howard F. Root, in 1934. At that time, he found it was 13 times as great in our diabetic group as in the comparable group of school children in Massachusetts. Therefore, we know how near the danger is. Incidentally, he also showed the extraordinary frequency of tuberculosis following recovery from diabetic coma in our own coma series. He found that within three years following recovery from coma, one in eight of our patients developed tuberculosis of the lungs. Since it happens that 10 per cent of our diabetic children at one time or another go through an attack of diabetic coma we have here a predisposing factor. But tuberculosis does not originate *de novo* and Dr. Root tells me that among these nine deaths from it in our children's series there was obvious exposure in four instances.

How shall this second group of needless deaths of diabetic children be averted? 1. Remembering the high incidence of tuberculosis in diabetic children much more energy should be expended both to prevent it and to detect it early. It is not a question of skill, but plain hard work and the use of well known methods. Tuberculin tests should be done yearly and if positive followed up by roentgen-rays. Moreover these rules should apply increasingly as long as the patients live. It costs us doctors nothing to secure a Wassermann test for our diabetic children and we never fail to take such, although as yet we have never had one positive. To secure a roentgenogram of the chest of a child, however, entails an expense which may reach \$15. The means for securing roentgen-rays should be simplified.

*Infections.* Infections apart from tuberculosis have claimed 17 diabetic children and in a rising percentage for the three five-year periods from 9 to 11 to 26 per cent. Elsewhere when the follow-up of all our children for 1937 is complete, we shall report these in detail.

*Hypoglycemia.* Hypoglycemia was responsible for four deaths. These cases already have been reported elsewhere. The first was soon after the discovery of insulin, far from Boston, and in an excellent hospital. The poor little child was wasted with a long standing infection, had undergone a multitude of therapeutic procedures; blood sugar tests were then made only with venous blood and what proved to be the crucial test, I understand, was postponed with the best intentions by a tender-hearted house officer until too late. The second death was in a child who sang in the choir Sunday night, had a convulsion the following morning at 2 a.m. and the

diagnosis being mistaken for diabetic coma received 200 units of insulin from a doctor who had never seen a case of coma or of an insulin reaction and at the moment was caring for a pregnant woman. Details about the other two are unsatisfactory and hypoglycemia was not demonstrated.

*Miscellaneous.* In this group are included two deaths by trauma and one reported as cerebral hemorrhage. There are also two deaths during pregnancy.

Pregnancy occurs rather frequently among our girls who have outgrown childhood and although it can be successfully undergone there are real risks unless the greatest precautions for care during its course and at delivery are taken. Among our group of girls with onset of diabetes in childhood and now above the age of 18 years we know of at least 28 instances of pregnancy. We do know that in 26 the result was without harm to the mother, but there were two deaths—7 per cent—or fully 14 times the standard rates! Elsewhere these cases will be reported in detail by my colleague, Dr. Priscilla White.

#### CONCLUSIONS

When one contemplates the mortality of these children and realizes that 82 of them, 79 per cent, died needlessly—69 of coma, 9 of tuberculosis, 4 of hypoglycemia—and possibly that some of the others might have been saved with more alert and expert treatment during their infections or pregnancy, it is evident that the present mortality of diabetic children is a remediable and therefore a hopeful index of the future of the diabetic child.

August 7, 1937, begins the fourth quinquennium since my use of insulin and at its end I am confident a brighter report can be made than hitherto. It demands no new discovery, but only that same persistent, individual and educational effort for each child which Dr. Joseph H. Pratt displayed in the organization of his first tuberculosis class. That class suggested to me the educational methods which I have employed in the treatment of my diabetics and it is a satisfaction to record here my whole-hearted and appreciative recognition of his help.

## EDITORIAL

### *POSTGRADUATE COURSES FOR MEMBERS OF THE COLLEGE*

A fundamental purpose of the American College of Physicians is to raise the level of the practice of internal medicine. Important steps have been taken towards the attainment of this objective.

The development of the membership of the College to include a majority of the more outstanding clinicians, teachers and investigators of this country has in itself been important since it increases the prestige attached to membership in the College. Membership in the College thereby becomes a natural goal of the ambitious young internist. Since membership is to be won by furnishing evidence of careful study, of teaching, of research, of publications as well as of high ethical standards in practice, the more the College attracts young men the greater will be the influence of the College upon the future standards of internal medicine.

In its participation in the establishment and in the direction of the American Board of Internal Medicine the College has again demonstrated its belief that the title of internist should connote definite and serious study, training and experience. The requirements made of the applicant are not rigid but to meet them will require a training which is broader and more intensive than that usually afforded by the medical internship and residency. In many instances such training has been too exclusively a bedside apprenticeship to a few senior clinicians plus a large quota of time devoted to the routine details of administration of a medical service. No provision has been made for orderly study of the pathologic physiology of disease, nor for advanced training in the methods of clinical pathological research. With the exception of a relatively few institutions most hospitals give to their Residents a type of training which was developed half a century ago when all the hospital had to offer was concentrated clinical experience. It is certain that the establishment of the various Boards for the specialties is actively stimulating a revision of the whole residency system. These vital years must be so reorganized as to give to the Resident more time for study, more systematic instruction, and a broader clinical experience than the average general hospital can furnish on its wards. Groupings of hospitals to furnish complete training, and alliances of hospitals with nearby medical schools offer possibilities worthy of consideration. A period of rotation in special out-patient clinics (cardiology, neurology, allergy, etc.) may often usefully supplement the ward and private patient experience of the Resident. It seems certain that in helping to establish the American Board of Internal Medicine the College has done a great deal to alter and improve the training of young internists.

These efforts of the College to raise the level of training for internal medicine are, however, only a part of its educational program. From the

earliest days the best known activity of the College has been its Annual Session; and what is the significance of this week-long meeting if it is not a wholesome acknowledgment of the fact that the need for medical education does not stop when Fellowship in the College has been attained? Indeed the College is made up of a fellowship of students—life long students of the art of medicine,—and not by any means of a faculty of instructors. It is this eager interest on the part of the Fellows for the latest and the best in medical knowledge that adds so greatly to the stimulating atmosphere of our Annual Sessions. During that time we are all students together in a temporary school of our own creation.

This year will witness one of the most valuable of the Annual Sessions, since for the first time since very early days we are to meet in New York and to have laid before us the tremendous resources and activities of its great medical institutions. It seems certain that there will be a gathering of the membership of record breaking proportions.

This year witnesses also an innovation—the establishment by the College of a group of Postgraduate Courses for Fellows and Associates during the two weeks preceding the Annual Sessions which begin on the fourth of April. Each Fellow and Associate has already received the preliminary announcement from the Committee on Postgraduate Courses appointed by the Regents. The courses are offered at Harvard and Columbia Universities and at the University of Pennsylvania. In addition to general medicine there are to be special courses in the neuropsychiatric aspects of medicine, in metabolism, cardiovascular diseases and gastrointestinal diseases.

It is only through trial efforts of this type that the needs and the desires of the members of the College can be discovered. The establishment of such timely opportunities, which extend the postgraduate study period of the Annual Sessions, is to be looked on as a logical development of the essential program of the American College of Physicians.

## REVIEWS

*The Diagnosis and Treatment of Pulmonary Tuberculosis.* By JOHN B. HAWES, M.D., and MOSES J. STONE, M.D. 215 pages; 14 × 21 cm. Lea and Febiger, Philadelphia, Pa. 1936. Price, \$2.75.

This brief and concise textbook on pulmonary tuberculosis, in our opinion, fulfills a very definite and until now unsatisfied need in this field. It confines itself to the essentials of the disease and does not include theoretical discussions of the intricate and highly specialized subjects of immunity, resistance, allergy, etc. The student is referred in an excellent bibliography at the end of each chapter to more complete and larger works.

There are sections on the history of the disease, on history taking, on physical examination, on constitutional and local symptoms, on childhood tuberculosis, on the treatment of the disease and on tuberculosis in pregnancy and in industry.

The authors show great ability to compress the discussion of facts into small space without losing clearness or interest. Mature experience has enabled them throughout to justly distribute the emphasis so as to enable the reader to discern between the essential and the less important facts.

This excellent book should be in the hands of every practitioner of medicine and should be a standard of instruction for medical students. The manner of presentation, the data given and the bibliography make it worthy of the attention of all interested in tuberculosis.

*Synopsis of Clinical Laboratory Methods.* By W. E. BRAY, B.A., M.D. 324 pages; 12 × 19.5 cm. C. V. Mosby, St. Louis. 1936. Price, \$3.75.

An amazing amount of valuable information is contained in this small volume. Included are: A chapter listing the usual tests required by the various general and special hospital services, chapters on urinalysis (including diagnosis of pregnancy), on hematology, blood chemistry, gastric analysis, feces and intestinal parasites, puncture fluid examination and cerebrospinal fluid, sputum, bacteriology, water and milk examination, serology, basal metabolism, allergy tests, poisons and foreign substances, surgical pathology, and a chapter of formulae and a table of normal values.

Precautions to be observed in the collection of specimens and performance of tests are emphasized. A succinct statement of interpretation follows each method given.

In a book which is so modern in all other respects it is unfortunate that the author adheres to the older bacteriological nomenclature. There are very few errors of statement or typography. The choice of technics included seems judicious.

The summary treatment of topics makes the book more valuable as a guide to the trained technician or as a supplement to more detailed works on the subject than for use by the inexperienced as a single source. It is highly recommended as a reference.

J. H. M.

*Developmental Abnormalities of the Eye.* By IDA MANN, D.Sc., M.B., B.S. (London), F.R.C.S. (Eng.). 444 pages; 16 × 24 cm. Published for the British Journal of Ophthalmology by the Cambridge University Press. 1937. Price, \$15.00.

This book is divided into eleven chapters. The first three deal with general considerations as to how abnormalities of the eye develop as well as general abnor-



malities of both the skull and the eye. Chapters IV and V are in reference to abnormalities of the fundi, VI of the iris, VII of the iris and vitreous, VIII of the lens, IX of the cornea, X of the conjunctiva and sclera, and XI of the lids, lachrymal apparatus and the orbit.

In her consideration of the subject Miss Mann has not only described congenital abnormalities but also those abnormalities that develop later. Her previous study of the embryology of the eye combined with the clinical material as seen in her own and her colleagues' clinics makes the work doubly authoritative. There may be some disagreement with the author concerning the theories advanced as to the mechanism of some of the developmental defects but those proposed seem quite logical.

The first three chapters which deal with the production of developmental abnormalities as well as abnormalities of the head and the orbit, will be of interest to anatomists, neurologists and internists. The remaining chapters are of more especial interest to the ophthalmologists and will help to elucidate many an obscure finding.

The book is most excellent in its illustrations of which about 50 are completely or partially in color. The printing is clear and while a few errors of spelling and reference are noted, the book is to be highly recommended.

C. A. C.

*The Roentgenologist in Court.* By SAMUEL WRIGHT DONALDSON, A.B., M.D., F.A.C.R. 230 pages; 15 × 24 cm. Charles C. Thomas, Springfield. 1937. Price, \$4.00.

This book is the result of much reading of the law in its relation to the practice of medicine, supported by extensive personal experience on the witness stand. It is a well written, concise and authentic work on a subject too often neglected by the busy physician. As its title implies, the book is supposed to concern itself primarily with the law in its relation to the roentgenologist, but the legal aspect of the practice of roentgenology differs very little from the practice of medicine in general, and consequently it contains very little that has not been said before. The chapters on "X-Ray Films and Evidence," "Ownership of Films" and "Conclusions" are of special interest to radiologists, but can be read with profit by every physician who is apt to be called upon to testify in cases where roentgen examinations have been made. Too much space has probably been given to the citation of selected cases and court decisions, that have but little bearing upon the medical witness. The increasing frequency of law suits and the blind faith that so many people place in the use of the x-rays, regardless of the qualifications and experience of the physician who made the examinations, bring the roentgenologist into court more frequently than many of his confrères. Any physician who is apt to be called as a witness will be sure to find his court experience less onerous after a careful perusal of this small volume. It is sure to find a welcome reception in the library of radiologists. It also contains much of value to members of the legal profession who are confronted in the court room with the presentation and interpretation of roentgen-ray films.

H. J. W.

*Vascular Disorders of the Limbs.* By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P.; Physician in Charge of Department of Clinical Research, University College Hospital, London. 111 pages; 16 × 22.5 cm. The Macmillan Company, New York. 1936. Price, \$2.00.

This small volume can be highly recommended to practitioners and students. In it are found simple methods of testing circulation to the limbs and descriptions of disorders affecting the circulation of the limbs such as embolism and thrombosis, post-ischemic contractures, arteriosclerosis, thromboangiitis obliterans, Ray-

naud's disease, acrocyanosis, erythrocyanosis and erythralgia. There are chapters dealing with the effects of circulatory arrest, arterial spasm, vasodilation and vascular disorders in diseases of the nervous system. The mechanisms and the treatment of these disturbances are described. Explanations of the maladies discussed are largely drawn from the author's researches published elsewhere. It should be noted that the author continues to attribute pain in circulatory arrest to the accumulation of products of muscular metabolism whereas evidence has been offered that this is not the sole factor. The book is remarkably condensed and at times this is annoying. One does not like to be referred to past or future discussions too frequently.

W. S. L., JR.

*Maternity and Post-Operative Exercises.* By MARGARET MORRIS, C.S.M.M.G. 152 pages; 22 × 13.5 cm., Oxford University Press. 1936. Price, \$2.00.

The author is the founder of the International Institute of Margaret Morris Movement, and states that she has intended the book primarily for masseuses, midwives, and nurses who have taken the diploma of the Institute. However, surgeons, internists, and especially obstetricians may read this book with profit.

There are seven chapters of which five comprise the text material, and the last two describe the exercises in diagrams and words, and give exercise charts for specific indications. There is no index. The book is well printed in pleasing form.

The indications, precautions, effects, and anatomic and physiological reasons for the various exercises are carefully described. Individual exercises are described in words accompanied by clear and easily understandable original outline drawings by the author. The basic importance of proper breathing during the performance of the exercises is stressed. All the exercises are gently progressive. A special group of corrective exercises is outlined.

It is hoped that the members of the medical profession will be interested in this book, since the author stresses that the exercises should be carried out under medical supervision.

J. E. S.

## COLLEGE NEWS NOTES

### GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

#### *Books*

- Dr. Jacob C. Geiger (Fellow) and Paul J. Hanzlik (Fellow), San Francisco, Calif.—“A Handbook of Accepted Remedies: Symptoms and Treatment of Poisoning; Diagnostic Procedures; Miscellaneous Information”;
- Dr. Raphael Isaacs (Fellow), Ann Arbor, Mich., and Dr. Hiram B. Weiss (Fellow), Cincinnati, Ohio—“Manual of Clinical and Laboratory Technic”;
- Dr. Frederick R. Taylor (Fellow), High Point, N. C.—reprints of Chapters XII-A on “Albinism,” XL-A on “Arachnidism: The Clinical Effects of Spider Bite” and XLIII-A on “Unusual Diseases and Symptom-Complexes not Discussed in Other Chapters (continued)” from the Oxford Loose Leaf Medicine.

#### *Reprints*

- Dr. Norbert Enzer (Fellow), Milwaukee, Wis.—1 reprint.
- Dr. William W. Graves (Fellow), St. Louis, Mo.—12 reprints.
- Dr. Paul J. Hanzlik (Fellow), San Francisco, Calif.—4 reprints.
- Dr. Elwood A. Sharp (Fellow), Detroit, Mich.—5 reprints.
- Dr. Barnett Greenhouse (Associate), New Haven, Conn.—1 reprint.
- Dr. Florimond LeBlanc (Associate), Elgin, Ill.—1 reprint.
- Dr. Robert P. Wallace (Associate), New York, N. Y.—1 reprint.
- Dr. John O. Woods (Associate), New Castle, Pa.—1 reprint.

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Dr. E. J. G. Beardsley (Fellow and Governor for Eastern Pennsylvania for the College), Philadelphia, was the guest of the Westmoreland County Medical Society at Greensburg (Pa.), on November 9. A clinic of patients exhibiting various cardiovascular disorders was held in the Westmoreland Hospital.

Dr. Beardsley also addressed the members of the Atlantic County (N. J.) Medical Society, Atlantic City, November 12, on “The Man of Fifty.”

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Dr. William R. Brooksher (Fellow), Fort Smith, has been appointed a member of the advisory council of the maternal and child health division of the Arkansas State Board of Health.

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The twelfth annual series of Friday Afternoon Lectures of the New York Academy of Medicine began November 19. The following Fellows of the College were scheduled to give lectures:

- November 19, Dr. Robert L. Levy, New York, “Drugs in the Treatment of Heart Disease”;
- December 17, Dr. Eugene M. Landis, Philadelphia, “Recent Advances in the Diagnosis and Treatment of Peripheral Vascular Diseases.”

Dr. Lewis B. McBrayer (Fellow), Southern Pines, N. C., has retired as managing director of the North Carolina Tuberculosis Association, which position he has held since 1915, when the association was founded. Dr. McBrayer also resigned as secretary of the Medical Society of the State of North Carolina.

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Dr. David I. Abramson (Associate), Brooklyn, has been appointed director of the department of cardiovascular research at the Jewish Hospital, Cincinnati.

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Dr. Alex. F. Robertson, Jr. (Fellow), Staunton, was elected president-elect of the Medical Society of Virginia at the annual meeting at Roanoke, October 12-14.

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Dr. A. Comingo Griffith (Fellow and Governor for Missouri), Kansas City, was recently elected president of the Jefferson D. Griffith Chapter of the Association of Military Surgeons.

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Dr. Elmer L. Sevringhaus (Fellow), Madison, Wis., and Dr. Arlie R. Barnes (Fellow), Rochester, Minn., were guest speakers at the annual meeting and clinical conference of the Southwestern Medical Association, held at Phoenix, Ariz., November 18-20.

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Dr. J. Arthur Myers (Fellow), Minneapolis, addressed the annual public meeting and "health crusade" of the District of Columbia Tuberculosis Association, November 22, on "Modern Methods in the Control of Tuberculosis."

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Dr. Elliott P. Joslin (Fellow), Boston, was a guest speaker on the dedicatory program of the new building of the Evangelical Deaconess Hospital, Detroit, November 10.

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Dr. Arthur M. Master (Fellow), New York, delivered the third of a series of lectures on heart disease, sponsored by the New York Heart Association, December 14, on "Use of Electrocardiograms in the Diagnosis and Prognosis of Coronary Thrombosis."

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Dr. S. Spafford Ackerly (Fellow), Louisville, was elected vice president of the recently organized Kentucky Psychiatric Association at a meeting in Lexington.

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The Northeastern Indiana Academy of Medicine was addressed at Kendallville, October 28, by Dr. Arthur E. Mahle (Fellow), Chicago, on "Recent Advances in Medical Management of Peptic Ulcer."

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At a meeting of the Hennepin County Medical Society, Minneapolis, November 10, Dr. Carl V. Weller (Fellow), Ann Arbor, spoke on "Intrinsic Factors in the Causation of Cancer."

Dr. J. Arthur Myers (Fellow), Minneapolis, president of the National Tuberculosis Association, was the guest speaker at the annual meeting of the New Jersey Tuberculosis League in New Brunswick, October 22.

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At the annual dinner of the Association for the Advancement of Industrial Medicine and Surgery, held October 20, Dr. Albert E. Russell (Fellow), U. S. Public Health Service, spoke on "Syphilis Control in Industry."

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Dr. B. B. Vincent Lyon (Fellow), Philadelphia, was a guest speaker at the sixth annual graduate program of the Summit County (Ohio) Medical Society. Dr. Lyon spoke on "Methods of Diagnosis and Treatment of Cholecystitis" and "Diagnosis and Management of Peptic Ulcer."

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Dr. Samuel B. Scholz, Jr. (Fellow), Philadelphia, was elected president of the Association of Life Insurance Medical Directors at the annual meeting in New York City recently.

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At its meeting in San Francisco in October, the Association of American Medical Colleges elected Dr. Willard C. Rappleye (Fellow), Dean of the College of Physicians and Surgeons of Columbia University, New York, as its president-elect, while Dr. William S. Middleton (Fellow), Madison, Wis., was elected vice president.

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The thirty-third annual meeting of the American Society of Tropical Medicine was held in New Orleans, November 30-December 3, in conjunction with the Southern Medical Association. Dr. George W. McCoy (Fellow) of the U. S. Public Health Service delivered the second Charles Franklin Craig Lecture on "The History of Leprosy in the United States." Another guest speaker at the sessions was Dr. William M. James (Fellow and Governor for Panama and the Canal Zone for the College), Panama, R. P., who spoke on "Emetine Therapy."

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Dr. Priscilla White (Fellow), Boston, was a guest speaker at the Fifth Annual Scientific Meeting of the Georgia Pediatric Society, December 9. Dr. White spoke on "Endocrine Problems in Juvenile Diabetes" and "Recent Problems in Juvenile Diabetes."

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Memorial rooms for the late Dr. Henry R. M. Landis (Fellow), Philadelphia, for many years director of the clinical and sociological departments of the Henry Phipps Institute, University of Pennsylvania, have been established in the suite he occupied at the Institute.

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The following Fellows of the College were guest speakers on the program of the Southern Medical Association's annual meeting at New Orleans, November 30-December 3:



- Dr. Stewart R. Roberts, Atlanta, Ga., "Your Health and Mine";  
Dr. Robert A. Cooke, New York, "Medical Problems of the Allergist";  
Dr. Priscilla White, Boston, "Protamine Insulin in the Treatment of Juvenile Diabetes";  
Dr. Walter C. Alvarez, Rochester, Minn., "Some Stages in the Development of Gastro-Enterology";  
Dr. Lawrence Reynolds, Detroit, "Pulmonary Cysts";  
Dr. William D. Cutter, Chicago, "The Appraisal of Medical Schools."
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Dr. Henry I. Klopp (Fellow), Allentown, Pa., has been superintendent of the Allentown State Hospital since its founding. On October 12 the twenty-fifth anniversary of the opening of the hospital was celebrated with a special program. Dr. James Allen Jackson (Fellow), Danville, Pa., presented a paper on "Extra-Institutional Clinical Activities in Twenty-Five Years." An oil painting of Dr. Klopp was unveiled as the gift of the medical societies of Lehigh, Northampton and Bucks counties and the Lehigh Valley Homeopathic Society.

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Dr. William Gerry Morgan (Fellow), Washington, D. C., was the chief guest speaker at the annual staff banquet of the Reading (Pa.) Hospital on November 3, 1937. Dr. Morgan was a resident intern at the old Reading Hospital in 1893. Memorials to two physicians, Dr. Charles H. Hunter, one of the founders of the hospital, and Dr. Charles G. Loose, for fifty-three years a member of the staff, and to Mr. Gustav R. Oberlaender, for many years President of the Board of Directors, were unveiled.

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Solomon Strouse (Fellow) has recently received the following appointments: Associate Clinical Professor of Medicine at the University of Southern California; Attending Physician at the Los Angeles County General Hospital; Visiting Physician at the Cedars of Lebanon Hospital, Los Angeles, California.

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Dr. William C. Voorsanger (Fellow), San Francisco, has been elected president of the San Francisco County Medical Society for the year 1938.

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Dr. David Riesman, Professor of the History of Medicine in the University of Pennsylvania, and Professor of Clinical Medicine in the Graduate School of the University, delivered the Vanuxem lectures at Princeton University on December 7, 8, 9 and 10. The lectures were on the general topic "Medicine in Contemporary Culture," the first being on "Medicine—Art and Science"; the second, on "Superstitions, Cults and Medical Ethics"; the third, on "The Family Doctor, Past and Future" and "Medicine as a Career"; the fourth, on "The Social Outlook in Medicine."

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Dr. Carl J. Wiggers (Fellow), Professor of Physiology, Western Reserve University, School of Medicine, has recently returned from the Orient, where he delivered a series of 16 lectures in Canton, Hong Kong, Shanghai, Peiping, Seoul, Kyoto and Tokyo. Professor Wiggers has accepted an invitation to address the Sixth National Congress of Medicine in Cordoba, Argentina, in October 1938, the other

guest speakers being Professor Gregorio Marañón from Madrid and Professor Volhard from Germany.

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The Annual Meeting of the Illinois Members of the American College of Physicians outside of Chicago was held at Bloomington, Illinois, on October 14, 1937, under the chairmanship of Dr. Samuel E. Munson, Governor. Dr. Edgar M. Stephenson and Dr. Gerald M. Cline served as a Committee on Arrangements. The meeting began at 3 o'clock in the afternoon and an interesting medical program was presented:

- "Arterio-Sclerotic Heart Disease," Dr. Nathan S. Davis, III, Chicago, Ill., Assistant Professor of Medicine, Northwestern University Medical School.
- "Current Endocrine Problems in Gynecology," Dr. Elmer R. Sevringhaus, Madison, Wisconsin, Associate Professor of Medicine, University of Wisconsin Medical School.
- "Peripheral Circulatory Failure," Dr. Louis M. Warfield, Milwaukee, Wisconsin, Former Professor of Clinical Medicine, Marquette University; Former Professor and Head of the Department of Medicine, University of Michigan.
- "The American Board of Internal Medicine, and Other Important Medical Questions," Dr. Walter L. Bierring, Des Moines, Iowa, Chairman, American Board of Internal Medicine; Past-President, American Medical Association.

Dr. Munson, as Chairman, reviewed for the Fellows of the College present the events of the last year in the history of the College and rendered a tribute to Dr. Frank Smithies whose death has occurred since the preceding Annual Regional Meeting, at which he had been present as a guest and speaker.

The afternoon program was followed by dinner at 6:30 and adjournment at 10:00 o'clock. The meeting was excellently attended by Fellows of the College from Illinois.

## ABSTRACT OF MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

*December 12, 1937*

A regular meeting of the Board of Regents of the American College of Physicians was held December 12, 1937, at the College Headquarters, Philadelphia, Pa., the meeting being called to order at 10:20 a.m. by President James H. Means, with the following present:

James H. Means, President  
William J. Kerr, President-Elect  
David P. Barr, First Vice President  
William D. Stroud, Treasurer  
George Morris Piersol, Secretary-General  
James B. Herrick  
Robert A. Cooke  
Jonathan C. Meakins  
Hugh J. Morgan  
James E. Paullin  
James D. Bruce  
Egerton L. Crispin  
James Alex. Miller  
Francis M. Pottenger  
Walter L. Bierring  
Ernest B. Bradley  
Roger I. Lee  
Sydney R. Miller  
Walter W. Palmer  
O. H. Perry Pepper  
Maurice C. Pincoffs  
Charles H. Cocke

and with the Executive Secretary, Mr. E. R. Loveland, acting as secretary of the meeting.

On motion by Dr. Paullin, seconded by Dr. Bierring and unanimously carried, the reading of the Minutes of the St. Louis Meeting was dispensed with.

Mr. E. R. Loveland, Executive Secretary, read communications from Dr. G. Gill Richards and Dr. William Gerry Morgan, the only absentees at the meeting.

The secretary also read several communications from public officials, physicians and one in particular from Dr. Willard C. Stoner, renewing the invitation from the City of Cleveland for the College to convene there in 1939.

The Executive Secretary further read a set of communications from public officials, the Academy of Medicine and, in particular, from Dr. Julien E. Benjamin, presenting an official invitation for the College to convene in Cincinnati in 1939. Mr. Loveland reminded the Board that invitations are still outstanding from New Orleans, San Francisco, St. Paul and Washington for 1939.

Dr. Ernest B. Bradley spoke in favor of the Cincinnati invitation, and expressed the opinion that Cincinnati's facilities and accommodations would be adequate for the College.

On motion by Dr. James E. Paullin, seconded by Dr. Sydney R. Miller and regularly carried, it was

*Resolved*, that the Executive Secretary be instructed to visit, in advance of the New York Session in April, any of the cities from which invitations have been received, in order to inspect their facilities and accommodations.

The Secretary brought to the attention of the Board that Dr. Clement R. Jones, of Pittsburgh, had presented a copy of the first edition and Dr. C. W. Waddell, of Fairmont, W. Va., had presented copies of both the first and second editions of the *ANNALS OF MEDICINE*, Volume I, 1920, to be added to the College archives. These were the first issues of the first journal sponsored by the American College of Physicians and the American Congress on Internal Medicine, but during the intervening years of changes in administration, all official copies of these issues had disappeared. The copies presented were in good state of preservation, and are a valuable addition to the College records.

On motion by Dr. Roger I. Lee, seconded by Dr. James E. Paullin, and regularly carried, it was

*Resolved*, that a vote of thanks be extended to the donors, Dr. Clement R. Jones and Dr. C. W. Waddell.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, read communications by Dr. George W. Pickering, of London, and Dr. Myron Prinzmetal, the 1936-37 Research Fellow, describing the work of Dr. Prinzmetal during the year—Dr. Pickering commending the College for awarding the Fellowship to Dr. Prinzmetal, and Dr. Prinzmetal expressing his deep appreciation to the College.

The following resolutions were unanimously adopted concerning the transfer of securities by the Treasurer some months previous:

*Resolved*, that the Treasurer of the American College of Physicians be and is authorized and directed, in accordance with the recommendations of the Finance Committee, to sell, assign and transfer fifty (50) shares General Motors common stock, Certificate No. C643-886, in the name of this corporation.

*Resolved*, that the Treasurer of the American College of Physicians be and is authorized and directed, in accordance with the recommendations of the Finance Committee, to sell, assign and transfer forty-five (45) shares Mid-Continent Petroleum Company stock, Certificate No. 7815, in the name of this corporation.

Pending the arrival of Dr. George Morris Piersol, Secretary-General, President Means reported the following deaths of members since the preceding meeting of the Board of Regents as follows:

*Fellows:*

Avery, Jacob Fowler	La Jolla, Calif.	June 25, 1937
Behlow, William Wallace	Palo Alto, Calif.	April 29, 1937
Betts, Arthur	Spokane, Wash.	October 17, 1937
Breed, Lorena M.	Pasadena, Calif.	October 20, 1937
Brown, Douglas	Castle Point, N. Y.	June 6, 1937
Chester, John Leonard	Detroit, Mich.	May 31, 1937
Crane, Augustus Warren	Kalamazoo, Mich.	February 20, 1937
Daland, Judson	Philadelphia, Pa.	August 14, 1937
Daley, Daniel Francis	Kingston, Pa.	April 24, 1937
Dalton, Eugene S.	Brooklyn, N. Y.	April 19, 1937
Dickie, Jamie W.	Southern Pines, N. C.	July 6, 1937
Eggleston, Elmer L.	Battle Creek, Mich.	July 7, 1937
Elrod, John Oscar	Forsyth, Ga.	April 21, 1937
Ferris, Albert Warren	East Orange, N. J.	October 4, 1937
Greiwe, John Ernest	Cincinnati, Ohio	October 29, 1937
Hardin, Ronda Horton	Banner Elk, N. C.	October 9, 1937
Howard, Leroy Taylor	M. C., U. S. Army	September 30, 1937

Landis, Henry R. M.	Philadelphia, Pa.	September 14, 1937
Lemann, Isaac Ivan	New Orleans, La.	September 2, 1937
Lyter, J. Curtis	St. Louis, Mo.	October 9, 1937
Mason, Elijah Lumbia	Washington, D. C.	August 30, 1937
McCampbell, Eugene F.	Columbus, Ohio	May 8, 1937
Miller, Joseph Leggett	Chicago, Ill.	August 6, 1937
Myers, Harold Bunce	Portland, Ore.	March 6, 1937
Oleson, Richard B.	Lombard, Ill.	August 6, 1937
Pothuisje, Peter Jurgens	Denver, Colo.	June 4, 1937
Samenfeld, Joseph	Brooklyn, N. Y.	September 5, 1937
Sherrill, Coite Long	Statesville, N. C.	June 24, 1937
Smith, Munford	Los Angeles, Calif.	June 28, 1937
Surnamer, Isaac	Paterson, N. J.	April 23, 1937
Sweet, Earl	Los Angeles, Calif.	May 22, 1937
Walcott, Harry Gilmer	Dallas, Tex.	June 2, 1937
Waples, Frank Alsworth	Houston, Tex.	March 4, 1937
Warr, Otis Sumter	Memphis, Tenn.	March 22, 1937
Wyckoff, John	New York, N. Y.	June 1, 1937

*Associates:*

Calhoun, Abner Wellborn	Atlanta, Ga.	November 3, 1937
Sprenkel, Vaughan LeRoy	Allentown, Pa.	June 18, 1937
Walker, Thomas Tipton	Watertown, N. Y.	November 13, 1937

President Means also, on behalf of the Secretary-General, reported the following additions to the Life Membership Roster since the last Regents' meeting:

Estella G. Norman, Miami Springs, Fla.  
 Charles W. Waddell, Fairmont, W. Va.  
 Hugh Francis Crawford, Memphis, Tenn.  
 Louise Taylor-Jones, McLean, Va.

These additions make a total of 83 Life Members, 4 of whom are now deceased, leaving a remainder of 79.

Dr. James E. Paullin, Chairman of the Committee on Public Relations, reported as follows:

## (1) Resignations of the following be accepted:

Colonel William Denton (Fellow), M. C., U. S. Army  
 Dr. D. Grant Campbell (Associate), Montreal, Que., Canada  
 Dr. George H. Jantzen (Associate), Queens Village, N. Y.  
 Dr. Frederick H. Lamb (Associate), Davenport, Iowa  
 Dr. Maurice T. Root (Associate), West Hartford, Conn.  
 Dr. Francis C. Weber (Associate), Newark, N. J.  
 Dr. James H. Wheeler (Associate), Henderson, N. C.

(2) That the request of Dr. George H. Spivey (Fellow), Hot Springs, S. D., to be dropped from the Roster be acceded to.

On motion by Dr. James E. Paullin, seconded by Dr. Jonathan C. Meakins, and unanimously carried, it was

*Resolved*, that the Board of Regents approve in full the recommendations of the Committee on Public Relations embodied in the three sections above.

Dr. Paullin, for the Committee on Public Relations, then reported that a "communication from Dr. Russell M. Wilder, of the Mayo Clinic, including a letter to Dr. James H. Means, President of the American College of Physicians, concerning



newspaper publicity in the *Chicago Daily Times*, has been received and read. Your Committee is in sympathy with the predicament in which the Mayo Clinic finds itself and with the embarrassing position in which they are placed, but it knows of no remedy which can be utilized to overcome such publicity."

On motion by Dr. Paullin, seconded by Dr. Jonathan C. Meakins and unanimously carried, it was

*Resolved*, that the Board of Regents approve of this part of the report of the Committee on Public Relations.

Dr. Paullin proceeded with his report: "A communication from Dr. Norman Strauss, of New York City, in which he propounds two questions and asks for an expression of opinion by the Board of Regents concerning a division of fees, has been received. It is the advice of the American College of Physicians that in professional dealings with patients, these be conducted openly and frankly, and that the principles of the medical ethics of the American Medical Association be followed, and that there shall be no fee-splitting and no attempt whatsoever made either at evasion or circumvention of these principles. Bills for medical services presented by various practitioners should be rendered separately, in order that no suspicion of motive be aroused. A copy of this reply to Dr. Strauss should be sent to Dr. Olin West, Secretary of the American Medical Association, Chicago, and to Dr. George E. Follansbee, Chairman of the Judicial Council of the American Medical Association, 629 Euclid Ave., Cleveland, Ohio, together with a copy of the Pledge, which each member of the American College of Physicians takes on induction into Fellowship."

On the suggestion of Dr. James Alex. Miller, the recommendation of the Committee was amended, providing for the insertion of the following: "Consequently, both questions submitted by Dr. Strauss are in violation of these principles."

On motion by Dr. Paullin, seconded by Dr. James Alex. Miller and unanimously carried, it was

*Resolved*, that the Board of Regents approve of the above section of the report of the Committee on Public Relations.

Dr. Paullin continued the report of his Committee: "A communication from Dr. Paul D. Abramson, Secretary of the Shreveport Medical Society (Shreveport, La.), was received and read. It is the opinion of your Committee that the American College of Physicians has no suggestion to make concerning this resolution (regarding an Act of their State Legislature constituting a State Hospital Board and opening charity state hospitals), and we respectfully refer the Shreveport Medical Society to the American Medical Association, who would properly have jurisdiction over such matters."

On motion by Dr. Paullin, seconded by Dr. F. M. Pottenger, and unanimously carried, it was

*Resolved*, that the Board of Regents approve of the above section of the report of the Committee on Public Relations.

Dr. Paullin proceeded with his report: "Your Committee is in receipt of a set of resolutions from the Committee of Physicians, of which Dr. John P. Peters, of New Haven, Conn., is the secretary, in which certain principles and proposals are outlined, and which have been signed by 430 physicians of the United States. We are also in receipt of another set of principles submitted by Dr. Eugene S. Kilgore, of San Francisco. In addition, there is a letter from Dr. Henry M. Thomas, Jr., Governor of the College for Maryland. Your Committee feels that these resolutions and proposals should be brought to the attention of the Board of Regents as a whole, without any recommendation of the Committee on Public Relations."

On motion by Dr. Paullin, seconded by Dr. Charles H. Cocke, and unanimously carried, it was

*Resolved*, that these proposals and recommendations be received and filed with the secretary.

Dr. David P. Barr, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, reported that the Committee is profoundly satisfied with the progress of the ANNALS, and while it is quite possible that various extensions of activity could be made, the work that the ANNALS is now doing seems to the Committee very good indeed, and, therefore, no specific recommendations were brought before the Board. However, he expressed the opinion that sooner or later the Editor would need additional help, particularly if new departments in the ANNALS are to be established. One of the matters discussed by the Committee was that of a department for postgraduate education, a service to internists and physicians throughout the country, which would keep them informed of postgraduate courses available here and abroad. There had also been some discussion of extension of monographs or special articles, similar to the one on rheumatism, which appeared several years in the ANNALS. The Committee in conclusion reported that in spite of a materially increased size of the ANNALS during the past year and, consequently, increased expenses, the ANNALS still is splendidly solvent.

On motion by Dr. George Morris Piersol, seconded by Dr. William D. Stroud, and unanimously carried, it was

*Resolved*, that the report of the Committee on the ANNALS OF INTERNAL MEDICINE be adopted.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, presented his report: "The Committee has considered 95 candidates for Fellowship and 183 candidates for Associateship. An analysis of the recommendations of the Committee concerning candidates for Fellowship is as follows:

47 to be advanced from Associateship
19 direct elections
14 to be advanced from Associateship 'as of April 3, 1938'
2 recommended for Associateship
8 deferred
5 rejected
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95

"An analysis of the action recommended by the Committee in connection with the candidates for Associateship is as follows:

146 elected Associates
2 elected Fellows
7 deferred for additional credentials
28 rejected
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183

Typed lists of all candidates were distributed for visé by each member of the Board of Regents."

On motion by Dr. Sydney R. Miller, seconded by Dr. James E. Paullin, and unanimously carried, it was

*Resolved*, that the following list of 68 be and herewith are elected to Fellowship in the American College of Physicians as of this date, December 12, 1937.

*Candidates**Sponsors*

## ALABAMA

Kyle Johnston Kinhead, Birmingham

James S. McLester, Seale Harris, Fred Wilkerson.

## CALIFORNIA

Joseph A. Pollia, Los Angeles

John V. Barrow, Samuel M. Alter, James F. Churchill.

Neville Thompson Ussher, Santa Barbara

Hilmar O. Koefod, F. M. Pottenger, James F. Churchill.

## COLORADO

Thomas D. Cunningham, Denver

J. N. Hall, James R. Arneill, Gerald B. Webb.

Edgar Durbin, Denver

James J. Waring, R. W. Arndt, Gerald B. Webb.

Lumir R. Safarik, Denver

Lorenz W. Frank, John G. Ryan, Gerald B. Webb.

Edwin Trueman Thorsness, Denver

Wilfred S. Dennis, W. Bernard Yegge, Gerald B. Webb.

## MEDICAL CORPS, U. S. ARMY

Sanford Williams French, Fort Washington, Md.

C. R. Reynolds.

## MEDICAL CORPS, U. S. NAVY

John Harper, Washington, D. C.

W. A. Bloedorn, P. F. Dickens, Dallas G. Sutton.

Frederick Leonard McDaniel, Washington, D. C.

Charles S. Butler, Walter Freeman, Dallas G. Sutton.

## DISTRICT OF COLUMBIA

Isaac Judah Silverman, Washington

Eugene R. Whitmore, C. B. Conklin, Wallace M. Yater.

## GEORGIA

Joseph Howard Hines, Atlanta

Russell H. Oppenheimer, H. Cliff Sauls, Glenville Giddings.

Champneys Holt Holmes, Atlanta

Allen H. Bunce, Trimble Johnson, Glenville Giddings.

## ILLINOIS

Lee Connel Gatewood, Chicago

Lowell D. Snorf, Arthur E. Mahle, James G. Carr.

## KANSAS

Fred John McEwen, Wichita

Henry N. Tihen, Harold W. Palmer, Thomas T. Holt.

## LOUISIANA

Willard Ralph Wirth, New Orleans

Randolph Lyons, John A. Lanford, J. E. Knighton.

## MARYLAND

Thomas Nelson Carey, Baltimore

M. C. Pincoffs, Louis Krause, Henry M. Thomas, Jr.

Richard France, Baltimore

Charles A. Waters, Sydney R. Miller, Henry M. Thomas, Jr.

Samuel Morrison, Baltimore

Julius Friedenwald, Theodore H. Morrison, Henry M. Thomas, Jr.

*Candidates**Sponsors*

John Arthur Foley, Boston  
Julian Carrel Gant, Boston

Francis Minot Rackemann, Boston

Olin Sewall Pettingill, Middleton

William Freeman, Worcester

Clement I. Krantz, Duluth  
Frank Hammond Krusen, Rochester  
Louis Elwood Prickman, Rochester

William Kendrick Purks, Vicksburg

Edward Hagerman Hashinger, Kansas  
City  
Delon A. Williams, Kansas City

Harold E. Himwich, Albany

Henry M. Feinblatt, Brooklyn

Arthur Edward Lamb, Brooklyn

William Henry Lohman, Brooklyn

James Moore Adams, New York  
Waldo Beattie Farnum, New York

Franklin M. Hanger, Jr., New York  
Harry Julius Johnson, New York  
John H. Keating, New York  
George Morris Lewis, New York

W. Laurence Whittemore, New York  
Abner Wolf, New York

Morris Eli Missal, Rochester

Thomas Preston White, Charlotte  
Herman Richard Parker, Greensboro

David Irvin Abramson, Cincinnati  
(formerly of Brooklyn, N. Y.)

## MASSACHUSETTS

Soma Weiss, W. B. Castle, William B. Breed.  
Dwight L. Siscoe, F. Dennette Adams, William B. Breed.  
J. O. Manier, George Morris Piersol, William B. Breed.  
Francis Joseph Welch, Edward Alfred Greco, William B. Breed.  
Erwin C. Miller, George M. Albee, William B. Breed.

## MINNESOTA

Frank W. Spicer, P. G. Boman, E. L. Tuohy.  
A. R. Barnes, E. V. Allen, E. L. Tuohy.  
E. V. Allen, Nelson W. Barker, E. L. Tuohy.

## MISSISSIPPI

W. N. Jenkins, L. J. Clark, G. W. F. Rembert.

## MISSOURI

Logan Clendening, Peter T. Bohan, A. C. Griffith.  
Harry L. Jones, Lindsay S. Milne, A. C. Griffith.

## NEW YORK

Harold Rypins, William Gerry Morgan, Walter W. Palmer.  
Tasker Howard, George H. Roberts, Jr., C. F. Tenney.  
Joshua M. Van Cott, Nathan T. Beers, C. F. Tenney.  
Tasker Howard, George H. Roberts, Jr., Robert A. Cooke, C. F. Tenney.  
Willard J. Denno, O. W. Bethea, C. F. Tenney.  
James R. Scott, Walter A. Bastedo, Walter W. Palmer.  
W. W. Herrick, W. P. Anderton, C. F. Tenney.  
Milton A. Bridges, Arthur C. DeGraff, C. F. Tenney.  
James R. Scott, W. P. Anderton, Walter W. Palmer.  
J. Homer Cudmore, David Stanley Likely, C. F. Tenney.  
Willard J. Denno, Russell L. Cecil, C. F. Tenney.  
Charles A. McKendree, Willard C. Rappleye, C. F. Tenney.  
Charles B. F. Gibbs, William S. McCann, Allen A. Jones.

## NORTH CAROLINA

Archie A. Barron, E. J. Wannamaker, C. H. Cocke.  
Frederick R. Taylor, D. Waldo Holt, C. H. Cocke.

## OHIO

J. Hamilton Crawford, George H. Roberts, Jr., C. F. Tenney.

*Candidates*

Harold Feil, Cleveland  
 Harley A. Williams, Cleveland  
 Augustus Alonzo Hall, Columbus  
 Clovis Litle McKibben, Toledo

*Sponsors*

J. M. Hayman, Jr., Howard T. Karsner, A. B. Brower.  
 Howard T. Karsner, J. M. Hayman, Jr., A. B. Brower.  
 J. J. Coons, John Dudley Dunham, A. B. Brower.  
 C. W. Waggoner, John T. Murphy, A. B. Brower.

## PENNSYLVANIA

Louis Borsch Laplace, Philadelphia David Riesman, Thomas M. McMillan, E. J. G. Beardsley.  
 William Gilmore Leaman, Jr., Philadelphia Robert G. Torrey, Martha Tracy, E. J. G. Beardsley.  
 Edward W. McCloskey, Philadelphia Josephus T. Ullom, T. Grier Miller, E. J. G. Beardsley.  
 Edgar Schall Henry, Sewickley Joseph H. Barach, Samuel R. Haythorn, E. Bosworth McCready.

## SOUTH CAROLINA

James Albert Bradley, Florence O. B. Mayer, J. Heyward Gibbes, Kenneth M. Lynch.

## TENNESSEE

Lucius Carl Sanders, Memphis Conley H. Sanford, Lyle Motley, J. O. Manier.

## VIRGINIA

William White Falkener, Newport News Edward L. Alexander, R. Finley Gayle, Jr., J. Morrison Hutcheson.  
 Paul Douglas Camp, Richmond Dean B. Cole, R. Finley Gayle, Jr., J. Morrison Hutcheson.  
 T. Dewey Davis, Richmond Dean B. Cole, C. M. Caravati, J. Morrison Hutcheson.  
 Harry Walker, Richmond William B. Porter, Porter P. Vinson, J. Morrison Hutcheson.

## WASHINGTON

Robert Leonard King, Seattle John M. Blackford, G. A. Dowling, Charles E. Watts.  
 Frank Rowe Maddison, Tacoma John M. Blackford, Lester J. Palmer, Charles E. Watts.

## WEST VIRGINIA

James Lewis Blanton, Fairmont C. W. Waddell, A. H. Stevens, Walter E. Vest.  
 Clement Coleman Fenton, Morgantown Edward J. Van Liere, G. R. Maxwell, Walter E. Vest.

## CANADA

*Manitoba*

John McFaul McEachern, Winnipeg J. C. Meakins, J. Currie McMillan, Fred Cadham.

*Ontario*

Frank Sparling Kennedy, London F. A. Willius, A. R. Barnes, Jabez H. Elliott.



*Candidates**Sponsors**Quebec*

David William McKechnie, Montreal	R. H. M. Hardisty, A. T. Henderson, D. Sclater Lewis.
Harold Nathan Segall, Montreal	Charles F. Martin, I. M. Rabinowitch, D. Sclater Lewis.

*Resolved*, that the following list of 14 be and herewith are elected to Fellowship in the American College of Physicians as of April 3, 1938.

## COLORADO

Alfred Roe Masten, Denver	Lorenz W. Frank, Paul J. Connor, Gerald B. Webb.
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## CONNECTICUT

Benjamin Horn, Bridgeport	Daniel P. Griffin, Charles H. Sprague, Francis G. Blake.
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## ILLINOIS

Samuel John Lang, Evanston	Arthur E. Mahle, Charles A. Elliott, James G. Carr.
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## LOUISIANA

Louis Anthony Monte, New Orleans	Ben R. Heninger, Edgar Hull, J. E. Knighton.
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## MISSOURI

Everett R. Deweese, Kansas City	George H. Hoxie, Peter T. Bohan, A. C. Griffith.
Ellis W. Willhelmy, Kansas City	Ferdinand C. Helwig, D. D. Stofer, A. C. Griffith.

## OHIO

Johnson McGuire, Cincinnati	William L. Freyhof, John H. Skavlem, A. B. Brower.
Clarence Elton Hufford, Toledo	L. A. Levison, C. W. Waggoner, A. B. Brower.

## PENNSYLVANIA

Bernard Isaac Comroe, Philadelphia	Simon S. Leopold, Charles C. Wolferth, E. J. G. Beardsley.
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## SOUTH CAROLINA

Robert Wilson, Jr., Charleston	Hillyer Rudisill, Jr., Francis B. Johnson, Kenneth M. Lynch.
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## TENNESSEE

Richard Edward Ching, Memphis	J. B. McElroy, William C. Chaney, J. O. Manier.
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## TEXAS

Walter Belknap Whiting, Wichita Falls	Henry A. Christian, O. B. Kiel, C. T. Stone.
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## UTAH

Fuller Bryan Bailey, Salt Lake City	G. G. Richards, O. J. LaBarge, L. E. Viko.
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## WEST VIRGINIA

Arthur Lee Osterman, Wheeling	D. A. MacGregor, William M. Sheppe, Walter E. Vest.
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*Resolved*, that the following list of 148 be and herewith are elected to Associateship in the American College of Physicians.

*Candidates**Sponsors*

Maurice James Abrams, Brewton

James O. Finney, Gadsden

David Barrow Snelling, Montgomery

Donald Frederick Hill, Tucson

John Nye Compton, Little Rock

Clarence Wilmott Olsen, Los Angeles  
Fletcher Brandon Taylor, Oakland

Rufus Anton Schneiders, San Diego

Hildahl I. Burtness, Santa Barbara

Gerald Robert Fisher, Colorado Springs  
John Leonard McDonald, Colorado Springs

Curtis Tuttle Prout, Hartford

George Adolph Wulp, Hartford

David Jerome Cohen, Meriden

Harold Strickland, Meriden

William H. Resnik, Stamford

## MEDICAL CORPS, U. S. NAVY

James Gillespie Dickson, Washington, D. C.

Bartholomew William Hogan, Washington, D. C.

Julian Love, Brooklyn, N. Y.

William Peter Mull, Washington, D. C.

Walter Johnson Pennell, Philadelphia, Pa.

Earl Richison, Newport, R. I.

## DISTRICT OF COLUMBIA

Alva Duckett Daughton, Washington

Leon Stuart Gordon, Washington

## ALABAMA

J. Harold Watkins, William H. Smith, Fred Wilkerson.

Hugh J. Morgan, John B. Youmans, Fred Wilkerson.  
J. Harold Watkins, Seale Harris, Fred Wilkerson.

## ARIZONA

W. Paul Holbrook, John W. Gray, W. Warner Watkins.

## ARKANSAS

John R. Dibrell, Charles H. Lutterloh, Oliver C. Melson.

## CALIFORNIA

Newton Evans, Percy T. Magan, James F. Churchill.  
Thomas C. McCleave, William H. Strietmann,  
Ernest H. Falconer.

Lyell C. Kinney, C. Ray Lounsberry, James F. Churchill.

W. D. Sansum, P. A. Gray, James F. Churchill.

## COLORADO

John A. Sevier, J. H. Brown, Gerald B. Webb.

John A. Sevier, G. Burton Gilbert, Gerald B. Webb.

## CONNECTICUT

C. C. Burlingame, O. G. Wiedman, George Blumer,  
Francis G. Blake.

John A. Wentworth, J. E. Hutchison, Francis G. Blake.

Thomas P. Murdock, William E. Hall, Francis G. Blake.

Thomas P. Murdock, William E. Hall, Francis G. Blake.

Chester S. Keefer, A. R. Felty, Francis G. Blake.

P. F. Dickens, Walter A. Bloedorn, Dallas G. Sutton.

C. S. Butler, C. W. Ross, Dallas G. Sutton.

C. S. Butler, C. W. Ross, Dallas G. Sutton.

C. R. Baker, G. E. Thomas, Dallas G. Sutton.

J. B. Helm, Joel J. White, Dallas G. Sutton.

Joel J. White, Otis Wildman, Dallas G. Sutton.

Lewis C. Ecker, Janvier W. Lindsay, Wallace M. Yater.

Tomas Cajigas, William Gerry Morgan, Wallace M. Yater.

*Candidates**Sponsors*

Hugh Hudson Hussey, Jr., Washington

M. W. Perry, Thomas S. Lee, Wallace M. Yater.

Theodore Ferdinand Hahn, Jr., DeLand  
Fred Mathers, Gainesville

## FLORIDA

Meredith Mallory, R. H. McGinnis, T. Z. Cason.  
George L. Cook, R. H. McGinnis, T. Z. Cason.  
Louie Limbaugh, L. B. McBrayer, T. Z. Cason.Albert Benjamin McCreary, Jackson-  
ville

## GEORGIA

Evert Abram Bancker, Jr., Atlanta

Trimble Johnson, Hal M. Davison, Glenville  
Giddings.

Albert W. Lewis, Jr., Atlanta

Russell H. Oppenheimer, John B. Fitts, Glenville  
Giddings.

Joseph Carey Massee, Atlanta

Hal M. Davison, Trimble Johnson, Glenville  
Giddings.

John Warrick Thomas, Augusta

V. P. Sydenstricker, Eugene E. Murphey, Glenville  
Giddings.

William Edward Storey, Columbus

H. Cliff Sauls, John B. Fitts, Glenville Giddings.

## IDAHO

Samuel Marshall Poindexter, Boise

Clyde R. Jensen, Cassius H. Hofrichter, Charles E.  
Watts.

## ILLINOIS

Clarence Lucas Gardner, Jr., Aurora

LeRoy H. Sloan, Joseph L. Miller (deceased), James  
G. Carr.James Alexander Walsh, Peoria  
Preston Vine Dilts, PittsfieldOrville Barbour, Fred M. Meixner, James G. Carr.  
Warren F. Pearce, Harold Swanberg, Samuel E.  
Munson.

William J. Bryan, Rockford

G. B. Lemmon, Leslie R. Webb, A. C. Griffith.

## KANSAS

Norman Reider, Topeka

William C. Menninger, Ralph M. Fellows, Thomas  
T. Holt.

## KENTUCKY

Ben Harvey Hollis, Louisville

Frank M. Stites, J. Murray Kinsman, C. W.  
Dowden.

Arthur Trimble Hurst, Louisville

Virgil E. Simpson, Sam A. Overstreet, C. W.  
Dowden.

John Stites, Louisville

William E. Gardner, Arthur Clayton McCarty, C.  
W. Dowden.

## LOUISIANA

Lang Floyd Holland, New Orleans

Edgar Hull, J. H. Musser, J. E. Knighton.

## MARYLAND

Conrad Acton, Baltimore

William S. Love, Jr., Paul W. Clough, Henry M.  
Thomas, Jr.

## MASSACHUSETTS

Walter Swan Burrage, Boston

Robert S. Palmer, F. Dennette Adams, William B.  
Breed.

Robert Titus Phillips, Boston

Louis M. Spear, John W. Dewis, William B. Breed.

*Candidates*

Thomas Van Orden Urmey, Boston  
 Lester Dow Watson, Milton  
 Joseph Victor Breen, Pittsfield

*Sponsors*

Chester M. Jones, Donald S. King, William B. Breed.  
 William D. Reid, Herman C. Petterson, William B. Breed.  
 James Z. Naurison, Paul D. White, William B. Breed.

## MICHIGAN

Bergein Marion Overholt, Battle Creek  
 Robert Johnson Needles, Detroit  
 Louis J. Steiner, Detroit  
 William Edward Jahsman, Ferndale

M. A. Mortensen, Charles E. Stewart, Henry R. Carstens.  
 F. Janney Smith, Frank R. Menagh, Henry R. Carstens.  
 Frank J. Sladen, John G. Mateer, Henry R. Carstens.  
 Robert H. Durham, Frank R. Menagh, Henry R. Carstens.

## MINNESOTA

Phillip Hallock, Minneapolis  
 Arthur C. Kerkhof, Minneapolis  
 Benjamin Bismark Blum, Rochester  
 Hugh Roland Butt, Rochester  
 Eric MacMillan Chew, Rochester  
 Charles Douglas Deeds, Rochester  
 William Roland Gibson, Rochester  
 Donald W. Ingham, Rochester  
 Walter Frederick Kvale, Rochester  
 Ferrall Harmon Moore, Rochester

Jay Conger Davis, Henry L. Ulrich, E. L. Tuohy.  
 S. Marx White, Moses Barron, E. L. Tuohy.  
 J. A. Bargaen, Albert M. Snell, E. L. Tuohy.  
 Walter M. Boothby, H. Z. Giffin, E. L. Tuohy.  
 E. V. Allen, F. W. Gaarde, E. L. Tuohy.  
 A. R. Barnes, H. L. Smith, E. L. Tuohy.  
 Albert M. Snell, James F. Weir, E. L. Tuohy.  
 F. A. Willius, A. R. Barnes, E. L. Tuohy.  
 E. V. Allen, F. W. Gaarde, E. L. Tuohy.  
 Nelson W. Barker, Edgar A. Hines, Jr., E. L. Tuohy.

## MISSOURI

Robert Emmet Britt, St. Louis  
 David B. Flavan, St. Louis

Ralph A. Kinsella, Charles Hugh Neilson, David P. Barr, A. C. Griffith.  
 J. Curtis Lyter, H. W. Soper, A. C. Griffith.

## MONTANA

Wayne Gordon, Billings

W. G. Richards, Edward J. Stieglitz, Louis H. Fligman.

## NEBRASKA

Esley Joseph Kirk, Omaha  
 Ernest Lynn MacQuiddy, Omaha

Rodney W. Bliss, Warren Thompson, Adolph Sachs.  
 Rodney W. Bliss, George P. Pratt, Adolph Sachs.

## NEW HAMPSHIRE

Nathan Townley Milliken, Hanover

Harry T. French, Francis G. Blake, Robert B. Kerr.

## NEW JERSEY

Joseph Joel Labow, Elizabeth  
 George Ginsberg, Hoboken  
 William G. Bernhard, Newark

Harry Bloch, Arturo R. Casilli, Clarence L. Andrews.  
 Harry J. Perlberg, Abraham E. Jaffin, Clarence L. Andrews.  
 John W. Gray, Edward C. Klein, Jr., Clarence L. Andrews.

*Candidates*

George C. Hamilton, Binghamton  
 John G. Senese, Brooklyn  
 Charles Windwer, Brooklyn  
 Edgar C. Beck, Buffalo  
 Francis Emmett Kenny, Buffalo  
 Elmer Alfred Kleefield, Forest Hills  
 Harry H. Epstein, Jamaica  
 Harold Lawrence Rakov, Kingston  
 Thomas Charles Healy, Luzerne  
 William C. Meredith, New Rochelle  
 Stanton Tice Allison, New York  
 Arthur Joseph Antenucci, New York  
 Samuel Harris Averbuck, New York  
 James McRae Bethea, New York  
 Norton Sager Brown, New York  
 Edward Arnold Burkhardt, New York  
 Emanuel Z. Epstein, New York  
 Frank Miller Falconer, New York  
 Charles K. Friedberg, New York  
 William Travis Gibb, Jr., New York  
 John Alexander Clinton Gray, New York  
 Edward B. Greenspan, New York  
 Paul Barrus Johnson, New York  
 Henry Bingham Kirkland, New York  
 Joseph Kovacs, New York  
 Putnam Crocker Lloyd, New York  
 Victor Wesley Logan, New York  
 Kirby Armstrong Martin, New York  
 Sylvan E. Moolten, New York  
 Herbert Pollack, New York  
 Henry Israel Shahon, New York  
 Solomon Silver, New York  
 Eugene S. Sugg, New York  
 Gurney Taylor, New York  
 Byard Williams, New York

*Sponsors*

## NEW YORK

C. H. Berlinghof, Victor W. Bergstrom, C. F. Tenney.  
 Joseph Samenfild (deceased), Charles S. Danzer, C. F. Tenney.  
 Harry R. Litchfield, Louis Harris, C. F. Tenney.  
 Howard Osgood, Harvey C. Schneider, Allen A. Jones.  
 Nelson G. Russell, Byron D. Bowen, Allen A. Jones.  
 Carl Boettiger, Goodwin A. Distler, C. F. Tenney.  
 Goodwin A. Distler, Charles M. Levin, C. F. Tenney.  
 Frederic W. Holcomb, Fred H. Voss, C. F. Tenney.  
 Carl R. Comstock, Morris Maslon, Walter W. Palmer.  
 Arthur F. Heyl, Warren F. Kahle, C. F. Tenney.  
 Edward P. Eglee, Grant Thorburn, C. F. Tenney.  
 Howard F. Shattuck, Thomas T. Mackie, Walter W. Palmer.  
 George Baehr, B. S. Oppenheimer, C. F. Tenney.  
 Asa L. Lincoln, Benjamin I. Ashe, C. F. Tenney.  
 Thomas T. Mackie, W. W. Herrick, Walter W. Palmer.  
 Asa L. Lincoln, Benjamin I. Ashe, C. F. Tenney.  
 George Baehr, Arthur M. Master, C. F. Tenney.  
 Howard F. Shattuck, Thomas T. Mackie, C. F. Tenney.  
 George Baehr, Arthur M. Master, C. F. Tenney.  
 W. P. Anderton, James R. Scott, Walter W. Palmer.  
 Howard F. Shattuck, Peter Irving, C. F. Tenney.  
 George Baehr, B. S. Oppenheimer, C. F. Tenney.  
 Milton J. Raisbeck, Joseph Lintz, C. F. Tenney.  
 Asa L. Lincoln, Benjamin I. Ashe, C. F. Tenney.  
 Irving S. Wright, A. Wilbur Duryee, Walter W. Palmer.  
 Thomas T. Mackie, W. W. Herrick, Walter W. Palmer.  
 Howard F. Shattuck, Arthur L. Holland, Walter W. Palmer.  
 W. P. Anderton, Thomas T. Mackie, Walter W. Palmer.  
 George Baehr, Arthur M. Master, C. F. Tenney.  
 George Baehr, Arthur M. Master, C. F. Tenney.  
 Walter G. Lough, F. Howard Westcott, C. F. Tenney.  
 George Baehr, B. S. Oppenheimer, C. F. Tenney.  
 Peter Irving, Howard F. Shattuck, C. F. Tenney.  
 Howard F. Shattuck, Thomas T. Mackie, C. F. Tenney.  
 Asa L. Lincoln, Benjamin I. Ashe, C. F. Tenney.



*Candidates**Sponsors*

Frederick William Williams, New York James R. Scott, Nathan B. Van Etten, Walter W. Palmer.

Arthur Douglas Redmond, Ogdensburg W. W. Hall, Henry P. Wright, Allen A. Jones.

Sutherland Eric Simpson, Watertown Walter Fox Smith, W. W. Hall, Allen A. Jones.

## NORTH CAROLINA

Andrew Blair, Charlotte

E. J. Wannamaker, J. P. Munroe, D. Heath Nisbet, C. H. Cocke.

Luther Wrentmore Kelly, Charlotte

E. J. Wannamaker, A. A. Barron, C. H. Cocke.

James Hubert McNeill, North Wilkesboro

P. P. McCain, S. M. Bittinger, C. H. Cocke.

## OHIO

Willard F. Machle, Cincinnati

Alfred Friedlander, David A. Tucker, Jr., A. B. Brower.

Charles Kenneth Riddle, Cincinnati

John H. Skavlem, David A. Tucker, Jr., A. B. Brower.

William Richard Hallaran, Cleveland

E. H. Cushing, Charles T. Way, A. B. Brower.

Robert Alvord Reading, Cleveland

Willard C. Stoner, V. C. Rowland, A. B. Brower.

## OKLAHOMA

Emry G. Hyatt, Tulsa

Russell C. Pigford, W. J. Bryan, Jr., Lea A. Riely.

## OREGON

Howard Phelps Lewis, Portland

Homer P. Rush, John H. Fitzgibbon, T. Homer Coffen.

## PENNSYLVANIA

Howard Kistler Petry, Harrisburg

Edward M. Green, J. B. McAlister, E. J. G. Beardsley.

Earl A. Daugherty, Philadelphia

Edward L. Bortz, Joseph T. Beardwood, Jr., E. J. G. Beardsley.

William Wallace Dyer, Philadelphia

Edward S. Dillon, Truman G. Schnabel, E. J. G. Beardsley.

Joseph Edeiken, Philadelphia

James E. Cottrell, Charles C. Wolferth, E. J. G. Beardsley.

Alexander Margolies, Philadelphia

James E. Cottrell, Charles C. Wolferth, E. J. G. Beardsley.

Henry F. Page, Jr., Philadelphia

Edward L. Bortz, Alfred Stengel, E. J. G. Beardsley.

Abraham Trasoff, Philadelphia

Thomas Fitz-Hugh, Jr., David Riesman, E. J. G. Beardsley.

Arthur Orr Hecker, Polk

Harvey M. Watkins, W. W. Richardson, E. Bosworth McCready.

## TENNESSEE

William Ramsey Blue, Memphis

Whitman Rowland, J. B. McElroy, J. O. Manier.

## TEXAS

Edward Paul Leeper, Dallas

C. M. Grigsby, David W. Carter, Jr., C. T. Stone.

Matthew Hill Metz, Dallas

David W. Carter, Jr., Henry M. Winans, C. T. Stone.

Ralph Howard Homan, El Paso

Orville E. Egbert, C. M. Hendricks, C. T. Stone.

Flavius Downs Mohle, Houston

Alvis E. Greer, David Greer, C. T. Stone.

Leon Charles Kopecky, San Antonio

Joseph Kopecky, Lee Rice, C. T. Stone.

<i>Candidates</i>	<i>Sponsors</i>
	VERMONT
Christopher Campbell Shaw, Bellows Falls	Harry R. Ryan, Dwight L. Siscoe, Paul K. French.
	VIRGINIA
Staige Davis Blackford, Charlottesville	H. B. Mulholland, J. Edwin Wood, Jr., J. Morrison Hutcheson.
Oscar Swineford, Jr., Charlottesville	H. B. Mulholland, J. Edwin Wood, Jr., J. Morrison Hutcheson.
Edward Bruce Mewborne, Newport News	Edward L. Alexander, Paul F. Whitaker, J. Morrison Hutcheson.
Kenneth Dawson Graves, Roanoke	Blanton P. Seward, George B. Lawson, J. Morrison Hutcheson.
Collins Denny Nofsinger, Roanoke	Blanton P. Seward, J. W. Preston, J. Morrison Hutcheson.
	WASHINGTON
Harold Julian Gunderson, Everett	Samuel F. Haines, James F. Weir, E. L. Tuohy.
George D. Capaccio, Seattle	Lester J. Palmer, G. A. Dowling, Charles E. Watts.
Miriam Lincoln, Seattle	Floyd R. Wright, William S. McCann, Charles E. Watts.
	WEST VIRGINIA
James Lowrance Wade, Parkersburg	F. C. Hodges, R. M. Wylie, Walter E. Vest.
Andrew Currence Woofter, Parkersburg	G. R. Maxwell, S. L. Cherry, Walter E. Vest.
	WISCONSIN
Llewellyn Rathbun Cole, Madison	J. S. Evans, William S. Middleton, Rock Sleyster.
	CANADA
	Alberta
Maxwell Mordcai Cantor, Edmonton	P. H. Sprague, D. M. Baltzan, Fred Cadham.
	New Brunswick
Robert Dickson Roach, Moncton	A. B. Walter, R. J. Collins, H. A. Farris.

Dr. Sydney R. Miller proceeded with his report: "The Committee on Credentials has reviewed 4 applications for reinstatement, and, after due consideration, moves the adoption of the following resolution:

"*Resolved*, that in accordance with the rules and regulations governing reinstatement, the following be and herewith are reinstated as Fellows of the American College of Physicians—Dr. Clarence Henry Beecher, Burlington, Vt., Dr. Gilbert E. Brereton, Dallas, Tex., Dr. William H. Stewart, New York, N. Y., and Dr. Julius Ullman, Buffalo, N. Y.

"The motion was seconded by Dr. Charles H. Cocke, and unanimously carried."

Dr. George Morris Piersol, Chairman of the Committee on Advertisements and Commercial Exhibits, reported as follows: "This Committee, after due consideration, has drawn up certain fundamental principles that they recommend for adoption to govern the College in the matter of exhibitors at the Annual Convention, namely:

"(1) Exhibitors shall be admitted on invitation only;

"(2) The initial approved 'Invitation List' shall be made up by the Committee and the Executive Secretary. Both the firm and the product must be approved.

Preference shall be given to exhibits of a scientific nature, such as pharmaceuticals, equipment and medical books;

"(3) Additions to the initial approved 'Invitation List' may be made by the Committee after application by firms, with the requirement that they submit complete literature concerning their products and their organization;

"(4) The 'Invitation List' may be revised annually on the recommendation of the Committee."

Dr. Piersol said that if such rules are adopted, it will give the Executive Secretary ample latitude in the regulation of exhibitors and in the exclusion of exhibits irrelevant to the practice of Internal Medicine or one of its allied specialties.

On motion by Dr. James E. Paullin, seconded by Dr. Roger I. Lee, and unanimously carried, it was

*Resolved*, that the recommendations of the Committee on Advertisements and Commercial Exhibits be approved.

Dr. Maurice C. Pincoffs, Chairman of the Committee on Revolving Loan Fund, reported as follows: "The Committee on Revolving Loan Fund, at a special meeting, has discussed in detail a project which we would like to submit at this time not for adoption, but for approval in principle, feeling that if it is thus approved, it will merit going into the laborious task of reducing it to a form where it could be considered and adopted at a later meeting. The Committee feels that the principle of establishing a Revolving Loan Fund is justified, because the College has added to the difficulties of young men preparing themselves for Internal Medicine, and there is danger that those difficulties may keep from Internal Medicine valuable men, both in character and ability. It is especially fitting, therefore, that the College should, within its means, attempt to aid that group of unknown size who may otherwise be deterred from going into Internal Medicine. We feel that we should attempt to aid them only insofar as we have or shall have added to their obstacles. In other words, if we consider, in a rough way, that we have added about two years to the average term of preparation, we should not attempt to carry a man through the whole period of training of five years, but only through the two additional years for which we have been responsible. It is also advisable because any longer period complicates the economics of the plan, and will be an undue burden of debt upon any young man who would wish to take advantage of it. The mechanism for putting the Loan Fund into effect is that this Board, or the President, as may be deemed advisable, appoint in each Class A medical school a representative from among those Fellows or Officers of the College that are attached to that school, who will assume the burden of forming his local committee to receive applications for aid from young men, either during their graduate work in that school or in that territory in other institutions. The filling out of blanks carefully, looking into the character and ability of the applicant and into his needs would fall upon each local committee. The application then should come to the standing committee, analogous somewhat to the Committee on Credentials. A standing committee of that type should meet semi-annually to consider applications coming from the different sections of the country, and pass upon them both in relation to their merit and to the funds available.

"Some preliminary study has been made of the question of funds and the manner in which a Revolving Loan Fund works (Dr. Pincoffs thereafter passed around a chart). To make it specific, a project has been worked out for four men, two for two years at \$1,000.00 a year each, and two for two years at \$500.00 a year each. This would entail an expenditure over a period of eleven years before the Fund would first become self-supporting, of somewhere around \$3,500.00 a year average. After eleven years, it would become somewhat better than self-supporting, and if at any time it should stop, the payments going on would pay back to the College in the course of another eleven years what had been put into it.

"It would be possible, with a sum approximating \$8,000.00 a year, to run units of a minimum of sixteen men. I say 'a minimum' because that figure of sixteen is based on our giving the maximum aid to each man, whereas it would be our endeavor to give such aid as should be urgently needed; probably the number aided would be far in excess of sixteen. I may say that this is felt to be in the nature of an experiment. I have consulted the Harmon Foundation, which has had a rather extensive experience in student loan work. As far as it is aware, there has been no loan fund of exactly this kind for graduate medical men, although some graduate medical men have received loans from funds devised for general aid for students. Our suggestion is in the nature of an experiment, which the College can cut short within a year, because the loans only extend over two years and the maximum amount is never such as would be crippling, and the yearly outlay, we feel, whether we start with \$4,000.00 or \$8,000.00, is something that our recent surplus could afford. The Committee feels that a more detailed plan in writing should be submitted to the Regents. The Committee, however, presents this interim report and hopes that the suggestion may be approved, if it seems feasible, or the plan discarded before any further work is put on it.

The College has been instrumental in adding to the requirements for entering Internal Medicine by raising its standards of admission to Fellowship and by initiating the American Board of Internal Medicine. It is felt that men will often require aid in their last two years before coming up for certification. The plan is based on allowing two years after certification before any beginning of repayment is made. The sum arbitrarily set for them to pay is at the rate of \$20.00 a month, or \$240.00 a year, which in the smaller loans enables them to make full repayment in a little over five years, and in the maximum loan, enables them to make repayment in ten years. It would never exceed ten years, and the Committee feels that it would often be under five."

There was general discussion of the report, with some consideration of the possibility of losses. From the experience of other loan funds, losses have been negligible, arising mainly due to death.

On motion by Dr. James Alex. Miller, seconded by Dr. James B. Herrick, and unanimously carried, it was

*Resolved*, that it be the sense of the meeting of the Board of Regents at the present time that the plan offers very interesting possibilities, and that the Committee be instructed to go ahead with the further details for the development of a completed plan.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, reported that the Committee had duly considered a number of names submitted as candidates for the John Phillips Medal. He read a list of the names of the men who had been considered, and discussed in particular the names of those who had been most seriously considered.

On motion by Dr. Barr, seconded by Dr. James E. Paullin, and unanimously carried, it was

*Resolved*, that the 1938 award of the John Phillips Memorial Medal be made to Dr. Harry Goldblatt, of Cleveland, Ohio, in recognition of his having devised an important method for the production and study of experimental hypertension in animals; for his having demonstrated the significance of renal ischemia in the causation of high blood pressure; and for his having contributed significantly to the understanding of essential hypertension, one of the most common and disabling conditions encountered in medical practice.

Dr. Barr proceeded with the second part of his Committee's report, in regard to a number of candidates considered by the Committee this year for the American College of Physicians' Research Fellowship. Only eight applications had been con-

sidered, and it was decided that the Committee would recommend only one Research Fellowship, this to be awarded to John Russell Smith, who, since his graduation, has served as Intern and Assistant Resident at the Barnes Hospital, St. Louis, and who has been engaged in research, most of the time, with Dr. W. B. Kuntz, in problems of circulation and respiration. His most recent work has been with Dr. Kuntz, conducting observations on peripheral vascular diseases. Dr. Smith desires to go to Professor Anrep in Egypt to pursue his studies, particularly of circulation and respiration.

On motion by Dr. Barr, seconded by Dr. W. D. Stroud, and unanimously carried, it was

*Resolved*, that a Research Fellowship in the amount of \$1,800.00 for 1938-39, beginning July, 1938, be awarded to Dr. John Russell Smith.

Dr. Barr reported that it was the hope of the Committee that in not presenting a candidate for the second Research Fellowship for 1938-39 that the fund may be so earmarked that the following year, given suitable candidates, the Committee might recommend three men instead of two.

Dr. O. H. Perry Pepper made the suggestion that the Committee consider doing something to find positions for the recipients of fellowships after the period of fellowship has expired. Dr. Barr was in agreement with this suggestion.

On motion by Dr. Barr, seconded by Dr. Jonathan C. Meakins, and unanimously carried, it was

*Resolved*, that the fund of \$1,800.00 not expended for 1938-39 for a second Research Fellowship be, nevertheless, appropriated for use for a third Fellowship during 1939-40, if desirable.

On motion by Dr. Barr, seconded by Dr. James E. Paullin, and unanimously carried it was

*Resolved*, that the College shall place at the disposal of each recipient of a Research Fellowship any part of the fund which the recipient may need at the beginning of his fellowship, so that it may be used for necessary expenditures in transportation, etc., subject to the recommendation of the Committee.

Dr. James Alex. Miller, Chairman, reported for the Committee on Future Policy for the Development of Internal Medicine:

"(1) The Committee recommends that the Regents request the Executive Secretary to look into the matter of liability insurance for members of the College from various angles and report to the Committee."

On motion by Dr. Miller, seconded by Dr. O. H. Perry Pepper, and unanimously carried, it was

*Resolved*, that the above recommendation be carried out.

"(2) The Committee recommends that the Board of Regents appoint a special committee to study the matter of graduate education in coöperation with the American College of Surgeons. Also, that the Regents consider the possibility of creating a standing committee on graduate education."

There was some discussion of this subject; Dr. Pincoffs spoke in favor of the idea of having a standing committee created, not necessarily of the Regents alone, but one including any member of the College particularly valuable for such work. Dr. James D. Bruce said that he would very strongly recommend that a committee of "this body be named, which can and may collaborate with the various national committees when and if their advice and assistance may be called for."

On motion by Dr. James Alex. Miller, seconded by Dr. Walter L. Bierring, and unanimously carried, it was

*Resolved*, that the Board of Regents authorize the appointment of a committee by the President of a size which he may select, not necessarily confined to members



of the Board of Regents, but to be designated as a committee of the Regents, on the whole question of graduate education and internal medicine.

On a further motion by Dr. Miller, seconded by Dr. James E. Paullin, and unanimously carried, it was

*Resolved*, that the whole matter of graduate education brought up by Dr. George Crile of the American College of Surgeons, together with his suggestions, be referred to this new Committee.

Dr. Miller, continuing his report, referred to a communication from Dr. Willard C. Stoner, of St. Luke's Hospital, Cleveland, Ohio, wherein the latter asked if from the special point of view of internists, the American College of Physicians could not do something looking toward the improvement of hospital standards similar to the activities now undertaken by the American College of Surgeons.

On motion by Dr. Miller, seconded by Dr. James E. Paullin, and unanimously carried, it was

*Resolved*, that it is the opinion of the Board of Regents that at the present time this College is not in a position to institute a program of this character.

Dr. William J. Kerr, Chairman, reported for the Committee on Postgraduate Survey. He stated that it was his opinion that the Committee had responsibility during the past year only to plan or arrange for special postgraduate courses. His Committee recommended that the College offer two types of courses, to be scheduled just before the Annual Session. The Committee had contacted Harvard University, Columbia University College of Physicians and Surgeons and the Graduate School of Medicine of the University of Pennsylvania. The Committee recommended a number of courses of two weeks' duration on such subjects as neurology, gastrointestinal diseases, cardiovascular diseases, etc. The Committee suggested, also, that Fellows of the College who attended these postgraduate sessions have their dues partially remitted, with the exception of the cost of the "Annals," and that Associates who attended the courses should have, perhaps, \$25.00 remitted on the cost of the course. It was the opinion of the Committee that such remittance of fees would tend to stimulate attendance. The Committee recommended that the Executive Secretary send out at once return postal cards to all members to determine their interest in these courses and how many would register, and that by the first of January, circulars concerning the courses, giving more details, should be distributed.

There was much discussion on the subject of remittance of dues and the cost of the courses. Dr. James D. Bruce suggested that there might be undertaken a longer range program of courses for those men preparing themselves for Associateship in the College. Dr. James Alex. Miller suggested that the remission be not in terms of dues, but in terms of the cost of the course, and that the courses should be given at a flat fee. Mr. Loveland, the Executive Secretary, proposed that admission to these postgraduate courses should be an added membership privilege; that the College should underwrite the entire promotional work of these courses, should handle all registration and collection of fees and that the College should reimburse the institutions in full for the cost of the courses. He suggested that all the printing and distribution of notices and all the clerical work connected therewith should be paid for by the College, so as to reduce the cost of the courses to the institutions. He emphasized the advisability of not withdrawing any courses announced, but to carry them through successfully, with any deficits made up by the College.

On motion by Dr. William J. Kerr, seconded by Dr. James E. Paullin, and unanimously carried, it was

*Resolved*, that the Committee be authorized to proceed with the development of the special postgraduate courses for the approaching New York Session, and that the expenditure in connection with the courses be limited to the necessary printing and clerical work attendant thereon.

Dr. O. H. Perry Pepper, Chairman of the House Committee, reported that that Committee had had no necessity for meeting, as nothing of importance had come up. The new College Headquarters have proved satisfactory in every way. The maintenance of the House has been agreeably low and has exceeded the maintenance of the former inadequate quarters by only a very small amount. He reported that a new floor would be laid in the General Office, appropriation for which already appears in the budget. He said that the House Committee is in search of a suitable painting to hang in the Board Room over the mantle, but that as yet no satisfactory one had been found, though negotiations were being considered for the purchase of the original painting of "The Country Doctor."

Dr. William D. Stroud, Treasurer, presented the following report, which upon motion, seconded and unanimously carried, was received and filed.

"Investments in Bonds .....	\$95,731.53
Investments in Stocks .....	23,233.60
Uninvested Cash in Endowment Fund .....	465.29
Cash in General Fund .....	21,957.49
"Estimated Income, 1937 .....	\$45,765.72
Estimated Expenditures, 1937 .....	27,595.61
Estimated Surplus, 1937, without adjustments .....	\$18,170.11
Adjustments:	
Add: Accounts Receivable, American Bd. of Int. Med. ....	3,816.31
Items paid during 1937, but chargeable against 1938—22nd Annual Session .....	2,592.61
	\$24,579.03
Deduct:	
Items received during 1937, but to be credited toward 1938 or later: ANNALS OF INTERNAL MEDICINE Subscriptions (Volumes XII and XIII) .....	130.53
ESTIMATED SURPLUS, 1937 .....	\$24,448.50
"Balances (November 30, 1937)	
Closed Banks:	
Bank of Pittsburgh .....	\$ 1,461.97
Exchange National Bank, Pittsburgh .....	1,166.14
Highland National Bank, Pittsburgh .....	3,081.22
	\$ 5,709.33
Open Banks:	
Girard Trust Co., Philadelphia .....	\$10,310.16
Provident Trust Co., Philadelphia .....	5,661.47
Royal Bank of Canada, Montreal .....	741.82
	16,713.45
	\$22,422.78

"As of November 30, 1937, the College has invested securities of a book value amounting to \$118,965.13; of this amount, \$63,308.98 is in the Endowment Fund and \$55,656.15 is in the General Fund; \$95,731.53 of the above amount is invested in bonds; \$14,736.25 is invested in preferred stocks and \$8,497.35 is invested in common stocks. In addition, the College has in bank balances (open banks) \$16,713.45, making a total of \$135,678.58."

Dr. James Alex. Miller, Chairman, made the following report for the Committee on Finance:

"The Finance Committee reports that the finances of the College are in excellent condition, with available surpluses for further investment, which they voted at the present time to invest, \$10,000.00, on advice of our Investment Counsel.

"We wish to express our appreciation of the great service that our Investment Counsel has been to us, that largely on account of their advice, the depreciation of our securities from their cost is only about 3 per cent, in spite of the very considerable

general depression in security value. The Finance Committee also reports that since the last meeting, there have been sold

50 Shares General Motors  
45 Shares Mid-Continent Petroleum  
70 Shares National Breweries, Ltd.

and there have been bought

150 Shares Pacific Gas & Electric  
50 Shares Chase National Bank  
50 Shares Continental Can, Preferred.

The income from all invested funds is at the rate of approximately 4½.

"The Finance Committee considered the various budgets which had been presented, and would recommend action under the different categories as follows:

Twenty-second <i>Annual Session</i> , President's Office .....	\$ 890.00
Twenty-second <i>Annual Session</i> , Executive Secretary's Office .....	9,423.33
Twenty-second <i>Annual Session</i> , General Chairman's Office .....	3,700.00
<i>College Headquarters</i> .....	4,961.00

The Executive Secretary had presented a budget in the amount of \$3,961.00. In addition, the Finance Committee recommends that a *Depreciation Reserve Fund* for the Real Estate account be set up for \$1,000.00 a year.

Executive Secretary's Office .....	20,675.33
ANNALS OF INTERNAL MEDICINE, Editor's Office .....	5,860.00
ANNALS OF INTERNAL MEDICINE, Executive Secretary's Office .....	19,621.67

\$65,131.33

JAMES ALEX. MILLER, *Chairman,*  
*Committee on Finance."*

By resolutions, the Board of Regents approved of the above report of the Committee on Finance, including the appropriations for the 1938 budgets.

It was the recommendation of Dr. James Alex. Miller that a Publicity Director be employed to control and supervise the publicity of the New York Session in 1938. An appropriation for the same had been included within the budget for the General Chairman. After extended discussion of the matter, in which Dr. Roger I. Lee expressed opposition to the proposal of obtaining full copies of each paper on the General Sessions and Special Lecture Programs, in connection with the work of the Publicity Director, on the basis of grave objections and inconvenience to the speakers and that the publicity, regardless of control, would never be acceptable any way, by resolution seconded and regularly carried, it was

*Resolved*, that the General Chairman, Dr. James Alex. Miller, be authorized to employ a Publicity Director for the New York Session, and that the General Chairman coöperate with the President in obtaining full manuscripts of each paper in advance of the Session where possible.

On motion by Dr. James E. Paullin, seconded by Dr. Jonathan C. Meakins, and unanimously carried, it was

*Resolved*, that for the guidance of the Publicity Committee press agents shall be excluded from both the clinics and roundtables at the New York Session.

Dr. Maurice C. Pincoffs suggested that an announcement should be made in the notices that go out concerning the General Sessions that it may be optional with the speaker whether or not his manuscript may be turned over to the press. Dr. F. M. Pottenger suggested that the notices also include a statement of the fact that the taking of tickets at all clinics and roundtables will be strictly enforced, and that this announcement also be made in the ANNALS OF INTERNAL MEDICINE, in connection with the program for the New York Session.

Dr. James H. Means, President, passed around a copy of the program of General Sessions and Special Lectures, and announced that the General Sessions would be held in the mornings, except Monday, rather than in the afternoons as has been customary. There is to be an afternoon General Session and an evening General Session on Monday, a morning General Session on Tuesday, Wednesday, Thursday and Friday. The Annual Business Meeting will be scheduled Thursday morning at 11:30. The Special Lecture program will be held in the afternoons from Tuesday to Friday, inclusive. The Convocation, as usual, will be held on Wednesday evening.

Dr. Means brought up for discussion the matter of adding more dignity and form to the Convocation when Fellowships are awarded. Dr. Reginald Fitz, the marshal of Harvard University, had made a number of suggestions at the Regents' dinner the night preceding, including the suggestion of all those on the platform, including Officers, Regents and Governors, wearing academic costumes.

In the discussion that ensued, a general suggestion was made that the Convocation program might be as follows: (1) Music on the Organ—processional, during which the Officers, Regents, Governors and newly elected Fellows, led by a marshal, will proceed to their respective places—the Officers, Regents and Governors on the platform and newly elected Fellows to a specially reserved section in the front of the hall; (2) Invocation; (3) Presentation of newly elected Fellows and a reading of the Pledge by the Secretary-General; (4) Conferring of Fellowships; (5) Presentation of the John Phillips Memorial Medal; (6) Annual address of the President; (7) Benediction; (8) Music on the Organ—recessional, during which the Officers, Regents and Governors and newly inducted Fellows, led by a marshal, shall retire from the hall. If any academic gowns shall be used, they shall be an official College gown, properly marked with the academic insignia already approved by the College, and special hoods shall be omitted. However, there was lack of agreement in many details, with the result that on motion by Dr. Ernest B. Bradley, seconded by Dr. James B. Herrick, and unanimously carried, it was

*Resolved*, that the whole matter of a revised plan for conducting the Convocation be laid upon the table.

However, the President was authorized to appoint a marshal for the Convocation, whereupon Dr. Means appointed Dr. Reginald Fitz.

Dr. James Alex. Miller, as General Chairman of the 1938 Session, reported on the program of Clinics, Roundtables and Entertainment. The clinics are to be concentrated at four hospitals, and accommodations for 2,700 physicians have been planned. He announced the program for the roundtables, stating that all of them would be conducted as luncheon-roundtables, and that facilities for 600 physicians per day had been arranged. He told of the plans of the Entertainment Committee, and announced that Mr. John W. Davis had been obtained as the Banquet speaker.

The Executive Secretary reported upon business arrangements for the New York Session, announcing that a blanket reservation had been made for seventy rooms for the Regents and Governors and invited speakers at the headquarters hotel, the Waldorf-Astoria. Special rates had also been obtained not only at the headquarters hotel, but at near-by hotels for members of the College attending the Session. He reported upon the plans for the Technical Exhibit, distributing copies of the charts and referring to the new plan of limitation of commercial exhibits to firms and products approved by the Committee on Exhibits of the College, excluding all exhibits irrelevant or non-scientific. He also announced the completion of the new Directory of the College during the past summer, with an improved plan with respect to the listing of Fellows and Associates. The new Directory contains the names of 2 Masters, 2,661 Fellows and 997 Associates, making a total of 3,660.

He also brought up the matter of a Post-Convention Cruise to Bermuda, sailing from New York on April 9 and returning to New York on April 15. Special rates

and accommodations are offered by the Bermuda-Furness Lines, using the S. S. Georgic and the S. S. Monarch of Bermuda at sea and the Hotel Bermudiana on shore. A cruise conductor for the steamship company would be in full charge of all arrangements, and the College will have no official duties or responsibilities, other than seeing that the best accommodations and advantages are offered to its members.

Dr. Walter L. Bierring, Chairman of the American Board of Internal Medicine, made the following report:

"This report is concerned, mainly, with a summation of the activities of the Board during the past year.

"1. Certification without examination:

At the meeting of the Board of December 11, 1937, 1,536 applications for Certification without examination were given final approval. This action was the result of many months of effort to obtain all available information regarding each applicant.

About 350 applications, after careful investigation, were found to have inadequate qualifications for certification without examination, and these applicants are being advised, with a few exceptions, to apply for admission to the written examination.

The certificate fee of \$10.00, that accompanied the application, is being returned in each instance.

The date limit for filing these applications had been announced as July 1, 1937.

"A limited number of applications has been received, 30, 60 and 90 days following the above date limit, and the Board at its meeting yesterday resolved that these applications be not considered as the lists were definitely closed.

"2. Certification by examination:

To July 1, 1937, 64 candidates have been certified by examination. Of this number, there were 35 who completed the practical examination in St. Louis, April 23, 1937, and 29 completed the practical examination in Philadelphia on June 5, 1937. The certificates have been forwarded to all of the successful candidates.

The following is a summary of the certification to date:

a. Certification without examination .....	1,536
b. Certification by examination .....	64
	<hr/> 1,600

"3. Examinations:

There were 80 candidates that appeared for the written examination held October 18, 1937, at thirty different medical centers throughout the United States and Canada.

The answer papers are being reviewed by the Committee on Examinations.

The next written examination is set for Monday, February 14, 1938, to be held in different centers.

The next practical examination will be conducted by members of the Board in New York City on Friday and Saturday, April 1 and 2, 1938, which is just preceding the meeting of the American College of Physicians, and another practical examination will be conducted in San Francisco in June, 1938, near the time of the annual session of the American Medical Association.



"The following action has been adopted by the Board:

"At a meeting in Philadelphia on December 11, 1937, the American Board of Internal Medicine reiterated its intention of inaugurating, with the approval of and at a date to be set by, the Advisory Board for Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association, a program of additional certification in certain of the more restricted and specialized branches of internal medicine.

"Candidates who have been certified by the American Board of Internal Medicine without examination, may apply in writing to this Board for further certification in one of the sub-specialties of internal medicine. Candidates who have been admitted to, and have successfully passed the written examination, Part A and B of Part I of the American Board of Internal Medicine, shall be eligible, upon application, for admission to an oral and practical examination in one of the sub-specialties of internal medicine.

"For the conduct of such special examination, it is planned that examiners appointed by the American Board of Internal Medicine shall be joined by examiners appointed by the National Society of the appropriate sub-specialty, when such a sub-specialty has been recognized by the Advisory Board for Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association as constituting a proper sub-specialty in internal medicine.

"Candidates who have successfully passed such a specialized Part II examination shall be certified by the American Board of Internal Medicine as possessing special training and qualifications for the practice of internal medicine in the special branch of medicine in which they were examined.

"It is hoped that the fact of their having passed such a special examination given in the manner outlined, may be recognized by the American Medical Association by appropriate symbols in the American Medical Directory.

"In financing the American Board of Internal Medicine during the period of organization and first year of operation, the American College of Physicians appropriated from its General Fund and advanced to the American Board of Internal Medicine the sum of \$8,816.31. At the April, 1937, meeting of the American College of Physicians, \$5,000.00 was refunded on this account, and a check for \$3,816.31, as final payment, is submitted herewith.

"The American Board of Internal Medicine extends to the Board of Regents of the American College of Physicians its appreciation for financial assistance and valuable counsel.

WALTER L. BIERRING, *Chairman,*  
*American Board of Internal Medicine."*

On motion by Dr. James E. Paullin, seconded by Dr. Charles H. Cocke, and regularly carried, it was

*Resolved*, that the report of the American Board of Internal Medicine be accepted with gratitude, and placed on file.

President Means announced that the next meeting of the Committee on Credentials would be held in Philadelphia on March 6, 1938; the next Regents' meeting at the Waldorf-Astoria in New York City on April 3, 1938, and that the Regents'-Governors' Dinner to be held at the Waldorf-Astoria on the evening of April 3, 1938.

Adjournment,

Attest: E. R. LOVELAND,  
*Executive Secretary.*

## OBITUARIES

## DR. RONDA HORTON HARDIN

Ronda Horton Hardin (Fellow), the son of Mr. and Mrs. H. J. Hardin, was born November 27, 1892 in Boone, N. C., and died at Banner Elk, N. C. October 9, 1937 from coronary thrombosis following a ruptured gastric ulcer six days previously.

After two years of premedical work at Trinity College (now Duke University), he graduated from the North Carolina Medical College in 1914. Postgraduate work was taken at Tulane University, Mayo Clinic, Cook County Hospital, Chicago, and the New York Postgraduate Hospital. On November 11, 1914, Dr. Hardin married Miss Eulalia Austin, the daughter of the late Dr. James A. Austin of Charlotte, N. C. Three children survive, Ronda H. Hardin, Jr., Jacqueline, and Margaret.

Dr. Hardin was head of the medical department of Grace Hospital, Banner, Elk, N. C. for a number of years, where his untiring zeal and efforts in ministering to the mountain people and others were outstanding features of this splendid institution, maintained by the Presbyterian Church. He was sometime President of the Avery County Medical Society, a member of the Tenth District Medical Society, of the Tri State Medical Society, composed of Virginia and North Carolina and South Carolina, Chairman of the Committee on Postgraduate Study of the North Carolina Medical Society, a member of the American Medical Association, and became a Fellow of the American College of Physicians December 1935.

Dr. Hardin was not a prolific writer, but a keen student of medicine. He produced one paper on the subject of Milk Sickness, a condition little seen outside certain restricted territories, the result of his own personal observations, and a valuable contribution.

He was quite interested in all civic affairs in his community, a member of Phi Beta Pi Medical Fraternity, and a deacon in the Presbyterian Church. Of modest and dignified bearing, Dr. Hardin's early passing at the age of 45 is a very distinct loss to the medical profession and to the entire community which he served so faithfully all of his medical career.

C. H. COCKE, M.D., F.A.C.P.,  
Governor for North Carolina.

## DR. J. CURTIS LYTER

Dr. J. Curtis Lyter (Fellow), of St. Louis, Missouri, died suddenly of heart disease, on October 9, 1937.

Dr. Lyter was born in Belmont, Ky., attended Smith's Classical School, Cynthiana, Ky., later attended the University of Missouri, where he received an A.B. degree. He received his degree of Doctor of Medicine from St. Louis University Medical School in 1907. Following this he served an in-

ternship at the Wabash Hospital, Moberly, Missouri, later entered general practice in Moberly, where he remained until 1915, at this time he located in St. Louis, Missouri, specializing in internal medicine. He was an instructor of Medicine, St. Louis University School of Medicine, formerly on the visiting staff of St. Louis City and St. Johns Hospitals, formerly Chief physician to St. Anthony's Hospital, later becoming a member of Missouri Baptist and Jewish Hospitals. Dr. Lyter was commissioned a captain of the Medical Reserve Corps in 1918, serving in the department for the study of cardiovascular diseases. He was a hard worker and took a great deal of interest in the St. Louis Medical Society and was the author of a number of publications. He was a member of the St. Louis Medical Society, The St. Louis County Medical Society, the Missouri State Medical Society. The American Medical Association, The Southern Medical Association, Fellow of the American College of Physicians, and a member of the Society of French Speaking Physicians of Europe and North America. He traveled extensively in the later years of his life and visited the large clinics of Europe.

Dr. Lyter will be greatly missed in the community where he has taken such an interest in the profession and in the affairs of the St. Louis Medical Society.

A. C. GRIFFITH, M.D., F.A.C.P.,  
Governor for Missouri

#### DR. HARRIE A. PATTERSON

Dr. Harrie A. Patterson (Associate) died at Fort Stanton, New Mexico, October 30, 1937, of pulmonary tuberculosis.

Dr. Patterson was born in Colleton County, South Carolina, in 1903. He received the degree of Bachelor of Science from the University of South Carolina in 1925, and in 1931 was graduated from the Medical College of the State of South Carolina. He was thereafter appointed Intern for duty at the U. S. Marine Hospital, New Orleans, La., where he served until June 1933, when he was transferred to Fort Stanton, N. M. In October 1935, Dr. Patterson submitted his resignation as an Intern in the United States Public Health Service. Later the same month, he was appointed an Associate Physician with the Veterans Administration for duty at Los Angeles, California. In March 1937, he was transferred by the Veterans Administration for duty at Tucson, Ariz., and in July of the same year, he was appointed as an Intern at the U. S. Marine Hospital at Fort Stanton, N. M.

Dr. Patterson made a number of contributions to the literature and was a member of the New Mexico Medical Society, the American Medical Association and the Medical and Surgical Association of the Southwest. He had been an Associate of the College since December 1936.

Furnished through the Courtesy of  
Division of Personnel and Accounts,  
United States Public Health Service

## DR. ARTHUR BETTS

Dr. Arthur Betts (Fellow) of Spokane, Washington, died suddenly on the golf course, October 17, 1937. Dr. Betts was born in Alexandria, South Dakota, February 1, 1892. He attended the University of South Dakota and was graduated from the University of Illinois College of Medicine in 1915. His internship was served in Cook County Hospital and following that he served in Camp Hospital No. 4, as pathologist and internist in 1918-19, in France.

After returning from Army Service, he located in Spokane and was roentgenologist for Deaconess and St. Luke's Hospitals from 1920 until his death. During this period, he achieved recognition as an outstanding man in his specialty and was elected to the American Roentgen-Ray Society, The Radiological Society of North America, The Pacific Coast Roentgen-Ray Society. He was a member of the Spokane County Medical Society and a Fellow in the American Medical Association.

At the time of his death he was president elect of The Washington State Medical Association. He had been a Fellow of the American College of Physicians since 1925.

The Profession of the State of Washington has suffered a great loss in the untimely death of Dr. Betts. His wise counsel and stable leadership would have been most valuable to us during the next two years. His genial and friendly bearing will be missed by all of those who were fortunate enough to count themselves his friends.

C. E. WATTS, M.D., F.A.C.P.,  
Governor for Washington

## DR. THOMAS COOK SMITH

Dr. Thomas Cook Smith (Fellow) died on December 14, 1937 in Louisville, Kentucky of chronic nephritis with uremia. He had been in ill health for two years or more but forced himself to continue work up until five weeks before his death.

Dr. Smith was born in Dublin, Georgia, 41 years ago. He received his early education in the Dublin High School and at Emory University. He graduated from Johns Hopkins Medical School in 1921 following which he became house officer in pediatrics at the New Haven Hospital, New Haven, Conn. He spent three more years there, ending up as Resident in Pediatrics. From New Haven he went to Louisville in 1925 as Instructor in Pediatrics at the University of Louisville Medical School. He played a very prominent part in the building up of the Department of Pediatrics at this Medical School, being at the time of his death, Associate Professor.

Dr. Smith entered private practice in 1926. As a physician he greatly endeared himself to his patients so that it may be safely said that at the time of his death he was one of the most beloved physicians in this section of the

country. Seldom has a doctor been taken into the hearts of his patients as was Dr. Smith. Although he did very little writing, yet he became known widely throughout this section of the country as an extremely competent pediatrician.

Apart from his private practice and medical school work, he was deeply interested in Public Health. He was Chairman of the Mental Hygiene Committee of the Community Chest and was one of the pioneers and leaders throughout his professional life in the mental hygiene movement, performing no small part in helping this movement to assume an important part in the civic life of his adopted city. He also had wide interests in other phases of community health work.

He belonged to the County, State and American Medical Associations. He was a Fellow of the American College of Physicians and of the Academy of Pediatrics. He was a member of the Innominate Society (a local society devoted to the study of the history of medicine). He was a member of the Helium Club and of the Conversation Club—a tribute to his conversational ability.

Apart from his patients, he had a host of friends as was evidenced by the daily procession of callers at his home during the first four weeks of his illness. He was a keen diagnostician and was frequently called on in consultation by specialists for his opinion concerning cases in their own particular fields of work. He was an omnivorous reader and a brilliant conversationalist. The profession and his city have lost a great man.

J. MURRAY KINSMAN, M.D., F.A.C.P.,  
Louisville, Ky.



## POST-CONVENTION CRUISE TO BERMUDA, FOLLOWING NEW YORK SESSION

Due to a widespread interest on the part of members of the College, arrangements have been made for a post-convention cruise to Bermuda, leaving New York on Saturday afternoon, April 9, following the close of the Twenty-Second Annual Session of the College in that city from April 4 to April 8. On two previous occasions post-convention features were arranged: (1) A post-convention cruise to Cuba and Panama, following the New Orleans meeting in 1928; (2) A post-convention tour of the Yosemite Valley, southern California and the Grand Canyon, following the San Francisco meeting in 1932. These proved so enjoyable, so inexpensive and so generally successful that the executive offices have agreed to cooperate again with members who are interested in another planned convention trip. Various possibilities in the way of cruises from New York City were considered, but the cruise to Bermuda was selected because it is one of the most attractive and restful spring-time trips; it requires only a few days and entails a comparatively small expenditure. No other place offered so much of interest and rest as the cruise to Bermuda. Space does not permit at this time or place of a full description of this charming island, its people, its climate, its magical caves, its sea gardens, its flowers and trees, its bathing and sailing and fishing, its golf courses and its many other attractions. A most interesting and attractive booklet, covering these features may be obtained from the cruise conductor.

## ITINERARY

- April 9—Sailing from New York about 3:00 P.M. on "The M. V. Georgic" of the Furness Bermuda Line. Tea, dinner, music, dancing.  
April 10—At sea. Bathing, deck sports, moving pictures, tea, music, dancing.  
April 11—In the early morning sail along the North Shore into beautiful Island studded Hamilton Harbor and transfer to Hotel Bermudiana. The day will be free for sight-seeing, sports or leisure.  
April 12—At the Bermudiana. Opportunity for sight-seeing, golf, bathing and other diversions.  
April 13—After breakfast a train trip along the Coast Route to St. George's; inspection of the old town; luncheon. In the mid-afternoon board the Monarch of Bermuda for the return voyage.  
April 14—At sea. Deck sports, bathing, bridge, tea, music, final dinner.  
April 15—Arrive New York about 9:00 in the morning.

AT SEA: Partially as a novelty and for the greater interest and experience of those taking the cruise, the "M. V. Georgic" will be used on the going journey and the "Monarch of Bermuda," one of the famous Furness twins—the handsomest and most perfectly equipped ship—will be used on the return trip. The "Georgic" is 712 ft. long, breadth 82 ft. and the gross tonnage 27,759. The "Monarch of Bermuda" is 580 ft. long, width 77 ft. and the gross tonnage 27,770. Both ships offer the maximum in luxury, modernity and comfort, security and stability. Superb service and excellent food are guaranteed.

ON LAND the Hotel Bermudiana will be used. It is located on a bluff overlooking both the town of Hamilton and the Harbor, and stands in its own spacious landscaped grounds.

INCLUSIVE PRICE: Special accommodations both on board ship and at the Hotel Bermudiana for members and friends of the College will be arranged. A cruise

conductor assigned to the College party will care for every detail. A part of the ship and a section of the Hotel will be set aside for the College party. Special reduced, inclusive rates covering the entire cost, including steamship ticket, hotel room and meals, transportation of baggage, alien head tax, Bermuda Government tax, U. S. Revenue tax, etc., are included in the following figures:

C Deck rooms outside, going on "Georgic," returning D Deck on "Monarch" *	\$116.25
B Deck rooms inside, going on "Georgic," returning C Deck on "Monarch" *	\$111.25
Outside rooms as above	126.25
Outside rooms with bath on "Georgic"	138.25
A Deck rooms inside, going on "Georgic," returning B Deck on "Monarch" *	\$116.25
Outside rooms as above	133.75
Outside rooms with bath on "Georgic"	151.25
Deluxe rooms and suites quoted on application.	
* All rooms on the "Monarch" have private bath and toilet.	

The decks on the two ships are lettered differently, but corresponding Decks are used in arranging the above categories.



The "Monarch of Bermuda" seen through the cedars from the Bermudiana Hotel grounds.

**EARLY BOOKING:** Because the post-convention cruise comes the week before Easter, it has been necessary to make a blanket reservation for the estimated group from the College. When these reservations are all taken up, it is improbable that any others can be obtained. This is especially true, not only on board ship, but at the Hotel Bermudiana. The conductor, therefore, urgently requests that members arrive at an early decision and make their bookings. The reduced cruise fares are guaranteed only to those booking long in advance of the Session. Those booking

earliest are assigned the best available rooms in the category so selected, and so receive the greatest discounts.

A DEPOSIT of \$25.00 holds your reservation and will be returned in full if your plans cannot be completed. These rates are good for this sailing to all members, their families and friends, who may wish to accompany them.



Stylish turn-out on a Bermuda Road.

For information, reservations, plan of the ship and other matters pertaining to the cruise, write to the Executive Secretary of the American College of Physicians, 4200 Pine Street, Philadelphia, Pa., or, preferably, directly to the cruise conductor, Mr. Leon V. Arnold, 36 Washington Square West, New York, N. Y.